ANNUAL REPORT
OF
PROGRAM ACTIVITIES
DIVISION OF RESEARCH GRANTS
DIVISION OF RESEARCH RESOURCES
DIVISION OF RESEARCH SERVICES

Fiscal Year 1980

U. S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service National Institutes of Health

ANNUAL REPORT

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United States. National Institutes of Health.

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HIGHLIGHTS

The Division processed 25,859 competing applications, 18,363 noncompeting applications, and 2,229 interim supplements during fiscal year 1980. Of these, 18,283 were assigned to DRG for review.

A central service unit was established to centralize the flow of paperwork through the Scientific Review Branch.

An electronic voting machine was field tested by five fellowship review panels. Further testing will ensue when modifications to the machine have been developed.

A series of four meetings was held in the fall of 1979 with the chairmen of all the NIH scientific review groups and key administrative personnel from NIH.

Increased stipends and changes in institutional allowances were announced.

The individual postdoctoral fellowship application form (PHS 416-1) was substantially revised.

Under authority of the National Research Service Award Act, a short-term training program for students in health professional schools was announced in October 1979.

The research grant application form (PHS 398) was revised in its entirety.

The NIH Annual Inventory of Clinical Trials was modified to reduce the reporting load.

The DRG Reference Room was disbanded after 20 years of operation because of space and staff limitations.

An extensive slide collection of the peer review process was developed.

Approximately 19,500 queries were processed through the IMPAC system during 1980, and 1,000 requests for information through the CRISP system.

OFFICE OF THE DIRECTOR

Dr. Carl D. Douglass, Director, spoke about the extramural programs at meetings of the Society for Artificial Internal Organs, New Orleans, Louisiana, April 17-18; the American Urological Association in San Francisco, California, May 18; the NIH meetings on the Minority Biomedical Support Program held in San Antonio, Texas, May 22; the Council of Graduate Schools in the United States at the University of Delaware in Newark, Delaware, July 17-18; and the Association of Independent Research Institutes in Boston, Massachusetts, September 10-12.

Dr. Douglass assisted in the NIH orientation on the peer review system for the Chinese Delegation sponsored by the World Health Organization, October 26 and November 2, 1979, and he co-chaired the meetings of the NIH Initial Review Group Chairmen held on November 19 and 27, and December 3 and 13, 1979.

Dr. Douglass is co-chairman of the committee on Grants Technical Assistants Standards; a member of the Performance Review Board; and the Competitive Research Grants Policy Group of the Department of Agriculture.

Dr. S. Stephen Schiaffino, Deputy Director, also participated in the NIH orientation on the peer review system for the Chinese Delegation sponsored by the World Health Organization and in the meetings of the NIH Initial Review Group Chairmen. In addition, he participated in the NIH Regional Workshop held in New Orleans, Louisiana, November 13-14, 1979; a Grantsmanship Seminar held in Baltimore, Maryland, March 20-21, and spoke at the annual meeting of the Society of Chairmen of Academic Radiology Departments, Tucson, Arizona, March 23-25. Dr. Schiaffino was a member of a committee established by the Fogarty International Center on the need to coordinate assignment and review and approval procedures for conference grant applications. He served on the Grants Technical Assistants Standards Committee, and participated in the Staff Training in Extramural Programs (STEP) forums during the year.

Dr. Samuel M. Schwartz, Associate Director for Scientific Review, presented a slide series on the NIH peer review system to Dr. H. G. Van Brummen, Netherlands Foundation for Medical Research, October 4, 1979, and to students of Old Dominion University, November 7. On October 26, Dr. Schwartz met with members of the Chinese Study Mission on Modern Organization and Management of Scientific Research and discussed the NIH peer review system. He participated in the Regional Conference on NIH Grants and Contracts held in New Orleans, Louisiana, November 13-14; the meetings of the chairmen of NIH scientific review groups, November 19 and 27, and December 3 and 13, 1979; two STEP modules, December 10, 1979, and May 15-16, 1980; a STEP Forum, January 15; and the STEP Annual Planning Meeting in Harpers Ferry, West Virginia, June 23; and presented a seminar on the NIH grants review and award process at the University of Arizona, February 12-15.

Dr. Schwartz is a member of a number of NIH committees such as the Grants Associates Board and Training Design Team.

Members of Dr. Schwartz's staff attended the Government Micrographics Conference at the Shoreham Americana Hotel, September 17-19, 1979, and the June round of DRG fellowship panel meetings at which the Consensor electronic voting machine was used. The staff are members of the Paperwork Management Committee, the Development of Audiovisual Materials Committee, the Executive Secretaries Handbook

Committee, the Grants Assistants' Handbook Committee, the Handbook of Referral Committee, the Revision of Instructional Material for Revisions, and the IRG Orientation Subcommittee. The staff also developed an extensive, ongoing slide collection about the NIH peer review system. This slide collection, which currently contains over 150 entries, has been used extensively for lectures and seminars by DRG personnel and by scientist administrators throughout NIH. In addition, the staff was actively involved in the preparation of a publication, NIH Extramural Programs, which will be made available by the Office of the Director, NIH, in the fall of 1980.

Staff of the Office of the Director had a major role in the revision of forms PHS 398 and 416-1 which were released to the scientific community in June and July this year.

The Division continued to meet the career development needs of the staff by encouraging participation in some form of formal training. Completion of individual training plans was requested of each employee and as a result over 200 employees enrolled in job related training courses. The number of those attending classes at the University of the District of Columbia as participants in the Upward Mobility Program rose to 15.

Two new EEO Counselors were appointed for the Division of Research Grants (DRG) at the beginning of the year under review. The Counselors attended the NIH EEO Counselor/Coordinator Orientation. This orientation informed new EEO Counselors of their roles and responsibilities while serving as EEO Counselors. In addition, the Counselors were provided with information on resources available to assist them in the effective performance of their EEO responsibilities. The EEO Counselors have completed the Basic and Advanced Equal Opportunity Counseling Courses, and the Federal Equal Opportunity Recruitment Program (FEORP) given by the Office of Personnel Management (OPM). The course is designed to provide agency officials with personnel and/or EEO responsibilities in developing and implementing affirmative recruitment programs.

The Counselors are ex-officio members of the Employee Advisory Committee (EAC), and work closely with the Division's delegate to the NIH Women's Advisory Committee (WAC). They inform and keep an open line of communication with the EAC and the WAC delegates.

The Counselors attended the EEO Advisory Council Annual Retreat held at Harpers Ferry, West Virginia, July 21-25, 1980, at which time they received a historical view of council activities, and significant achievements of the past year. The retreat was divided into two areas: the Council goals and objectives for the future, and Counselor training sessions conducted by the EEO Director for HHS.

Keynote speakers at the retreat were Dr. James Comer, Professor of Psychiatry, Yale University, and Dr. Alvin Poussaint, Associate Dean of Medicine, Harvard University. In addition, a consultant team headed by Larry Bonner, Division of Personnel Management, helped the Council look at the mechanisms for accomplishing the goals and objectives for the coming year.

Drs. Thomas E. Malone, Deputy-Director, NIH, and William F. Raub, Director, Extramural Research and Training, attended the final session. They gave the Council words of encouragement to move ahead and continue to have an effective EEO program at NIH.

EXTRAMURAL ASSOCIATES PROGRAM

The NIH Extramural Associates Program is in its second year of operation. Twenty Associates have participated to date. The Associates, selected competitively from among 30 applicants, represent institutions that contribute to the basic preparation of minorities and/or women for science. During their training they have had the opportunity to obtain on-site information about Federal health-related programs and related granting and contracting activities. Fourteen minority institutions (70 percent), 12 of which are predominantly black, and 3 women's institutions (15 percent) have been represented. Among the Associates, 12 (60 percent) have been minorities, and 6 (30 percent) have been women.

During fiscal year 1980, seven Extramural Associates, representing two women's institutions and four minority institutions, were on detail to the NIH. A listing of the seven Associates and their NIH advisors is attached.

Training And Work Assignments

Recommended core assignments included review and program experience at NIH and a series of 24 seminars for a total of 82 seminar hours. The seminars covered issues pertinent to the NIH grant and contract processes, as well as the research programs of other Federal agencies. The Extramural Associates who participated during the period February through July 1980 were also enrolled in the course, "Congressional Operations Seminar for Managers," offered by the Government Affairs Institute, Office of Personnel Management. As a result, this course will be added to the "core" curriculum for future Associates.

In addition to the recommended core assignments, working assignments were individually arranged in consultation with the Associates by their advisors. These assignments encompassed the major elements and concerns germane to the administration of Federal research programs, while focusing on the interests of the sponsoring college or university. At least one week was spent by each Associate in the office of sponsored research programs at either Georgetown University, the University of Maryland, or Howard University.

Staff Visits

Follow-up staff visits were conducted at five institutions whose representatives had already participated in the Extramural Associates Program. Through these visits, the EA Program Director and the former Associates' NIH advisors demonstrate NIH's continuing interest in the institution. They also assess the responsibilities of the former Associates in the institutional process of seeking external funds for research programs. Staff visit reports have been prepared for Hampton Institute, Hampton, Virginia; Paine College, Augusta, Georgia; St. Mary's University, San Antonio, Texas; Tuskegee Institute, Tuskegee, Alabama, and Wellesley College, Wellesley, Massachusetts.

Program Activities

The Deputy Director, NIH, and two Extramural Associates actively participated in the Fifth National Conference on Blacks in Higher Education sponsored by the National Association for Equal Opportunity in Higher Education (NAFEO). They discussed with Association members the opportunities available to participants in the Extramural Associates Program, as well as institution and NIH expectations. Interactions with NAFEO and its participant members are continuing.

The Associates who participated during the period February through July 1980 were active spokesman for the Program at the Minority Biomedical Support Symposium in Atlanta, Georgia. Following these initial contacts, letters were sent out to 25 individuals.

The Southern Regional Educational Board, Atlanta, Georgia, which among other activities administers trust funds for minority institutions, has identified appropriate institutional officials and distributed EA program brochures and updated program information to them. This relationship is expected to continue.

In September 1980, a revised program announcement will be distributed to administrators and influential faculty members of minority and women's institutions. Applications for the program will be accepted for the two 6-month periods beginning July 1981 and February 1982.

Fiscal Information

The budget for FY 1980 was $360,000 most of which is obligated under object classification code 25.9Y--other contractual services--for salary, travel and per diem reimbursements to participating institutions.

GRANTS ASSOCIATES PROGRAM

In this, its 18th year, the Grants Associates Program has graduated a cumulative total of 137 people: 118 males (86 percent) and 19 females (14 percent); of whom 16 (12 percent) were minorities.

Fourteen Grants Associates were on duty this fiscal year (6 females - 43 percent; and 8 males - 57 percent). Of these 14, only one (7 percent) was minority--Spanish surname. Three, 21 percent, came from the NIH intramural programs. Seven were entered on duty and another 6 were graduated this fiscal year. (1 GA's EOD date was at the end of FY 79 and his completion date will be at the beginning of FY 81; hence he was neither entered on duty nor graduated in FY 80). All 6 graduates accepted positions within the NIH: one each in NEI, NIA, NHLBI, DRG, and two in NIDR.

The Grants Associates Board chairperson this year was Dr. Suzanne S. Stimler, Director, Biotechnology Resources Program Branch, DRR. The vice-chairman, Dr. Samuel Schwartz, Associate Director for Scientific Review, DRG, will succeed her.

In pursuit of an even stronger Affirmative Action Plan, the GA Program announcement will appear in the Journal of the National Medical Association, The Chronicle for Higher Education and Urban Health--The Journal for Health Care in Cities, in addition to the five other journals and newsletters with a high density of women and minority scientist subscribers. Still further, a more formal approach has been taken in recruiting women and minority scientists from various national meetings at which there are large groups of women and minority scientists. For this year these meetings included: Federation of American Societies for Experimental Biology, Organization for Black Scientists, Minority Access to Research Careers, the American Society for Microbiologists, the Minority Biomedical Support Program and the National Medical Association.

Former or current GA Board members or former GAs attending these meetings acted as spokesmen for the GA Program and were provided with program information for distribution. Direct contacts then were made between those interested and the GA Program executive secretary.

Twelve GAs took a total of 44 courses (15 separate courses) for a combined total of 1,472 hours of training at a tuition cost of $7,007 (compared with last year's cost of $4,742). The average GA took 3.7 courses or 122.7 hours training at an average cost of $ 584 each. The Grants Associates had available 39 seminars in their Series for a total of 160 training hours. Budget restrictions prevented a site seminar at a regional office. When courses are added to the Seminar Series, then formal training represented only 7.06 work weeks or 13.6 percent of the GA year in training and 86.4 percent in on-the-job assignments. Last year's figures were 15 percent and 85 percent respectively. Hence, despite the amount of seminars and other coursework, formal training consumed a small percentage of the GA year.

This year 31 nominations were received from intramural and extramural scientists for participation in the GA Seminar Series. They represented nine institutes and three divisions within NIH and one from FDA. Twenty-two nominees were selected for participation representing each nominating component. Attendance this year was excellent. The Series this year added the following new seminars: the Office of Technology Assessment, the National Center for Health Services

Research, the National Center for Health Statistics, Interagency Regulatory Liaison Group, and a panel discussion on: "Interaction with the Scientific Community" with representatives from grants and contracts in both program and review. There was also an increase in the frequency of the panel presentation format which proved useful for the group.

The Directory of Graduated Grants Associates has been updated for publication this year. The Directory has proven valuable, particularly in recruitment and publicity, and has been informative for applicants, those interested in the Program, and for seminar speakers.

GRANTS ASSOCIATES FISCAL YEAR 1980

Name & Institution	NIH Advisor
Dr. Verna R. Lawson Associate Professor of Biology Chairman, Division of Science and Mathematics Bethune-Cookman College Daytona Beach, Florida	Dr. Francis Mahoney Radiotherapy Development Branch DCT, NCI
Dr. Martin Berlinrood Associate Professor of Biological Sciences Goucher College Baltimore, Maryland	Dr. J. Buckminster Ranney Deputy Director, Communicative Disorders Program, NINCDS
Dr. Phillip L. Young Professor of Biology Associate Dean, College of Arts Sciences Grambling State University Grambling, Louisiana	Ms. Barbara Bynum Assistant Chief for Special Review, SRB, DRG
Dr. Cecil Payton Associate Professor of Biology Chairman, Department of Biology Morgan State University Baltimore, Maryland	Dr. Clarice Reid Chief, Sickle Cell Diseases Branch DBD, NHLBI
Dr. Gary VanDenbos Associate Professor of Biology Northeastern State University Tahlequah, Oklahoma	Mrs. Juanita Cooke Director, Office of Special Concerns, NHLBI
Mr. Ruben E. Matos-Perez Dean of Administration Puerto Rico, University of Medical Sciences Campus San Juan, Puerto Rico	Mr. George Jarboe Executive Officer, DRG
Dr. Elaine Jacobson Assistant Professor of Biology Texas Woman's University Denton, Texas	Dr. Samuel Schwartz Associate Director for Scientific Review, DRG

OFFICE OF GRANTS INQUIRIES

Telephone and written inquiries on NIH research and training support mechanisms, research programs, and requests for data on NIH-supported research that entailed manual or computer runs on different research areas or disease entities remained at about the same high level as in previous years. Forty-five congressional inquiries, other than those for publications, were responded to by letter or telephone. Several press releases on availability of publications and senior staff appointments were prepared during the year under review.

There has been at least a 50 percent increase in the requests for research grant and individual postdoctoral fellowship award application forms following the announcements in June and July of the availability of the revised application kits for both mechanisms of support. The demand is expected to level off when supplies are readily available in the central control offices of the grantee institutions.

The staff designed and prepared an organization and function pamphlet for the Division; revised the fact sheet, National Institutes of Health Grants and Awards; compiled a handbook of financial aid programs for minorities, women, and the handicapped, and updated publications such as the Scientific Directory and Annual Bibliography, the NIH Almanac, and documents submitted by the Library of Congress and non-Federal organizations, and edited and prepared for publication the quarterly listings of new grants and awards for dissemination to the Congress, the press, and the general public.

There continued to be a steady demand for documents disseminated by the Office: NIH Advisory Groups, Basic Data Relating to the National Institutes of Health, NIH Guide for Grants and Contracts, listings of new grants and awards, and articles on the review process the most frequently requested. The demand for a comprehensive publication describing the NIH extramural programs has continued and the lack of such a document has been a deterrent to reducing the workload of the limited staff.

Viewings of the DRG slide series, How a Research Grant is Made, were arranged for visitors from grantee institutions. The slide series was also shown on request to new staff members and scientists from the BIDs. Because the series is out of date and has outlived its usefulness, the OGI staff designed and prepared a script for an animated videotape revision of the series for review by the Director and DRG senior staff. When it is completed, the videotape presentation will be invaluable to the OGI and hopefully to NIH personnel who present seminars on the extramural review and evaluation process.

Several representatives from instrument manufacturing and biomedical supply firms were briefed throughout the year on the CRISP and IMPAC systems. The CRISP and IMPAC videotape presentations prepared by the Statistics and Analysis Branch last year were helpful for both staff and visitors in describing the systems.

The Acting Chief continued to serve as the Division's Freedom of Information Coordinator and Acting Privacy Act Coordinator and was responsible for the preparation of quarterly and annual reports on DRG's compliance with the requirements of the Privacy Act and the Freedom of Information Act.

To enable senior DRG staff to prepare data for NIH Management on the volume of requests under the provisions of the Privacy Act, the OGI collected copies of all incoming letters addressed to the Division staff requesting summary statements and critiques on their grant applications before council review. The 3-month study was coordinated by the NIH Privacy Act Coordinator with similar requests to the institutes for presentation to the NIH Director early in the year.

The Acting Chief attended a 1-day seminar on writing position descriptions in the FES format.

OFFICE OF RESEARCH MANPOWER

Two important developments in the training area in fiscal year 1980 were the increase in stipends and changes in institutional allowances. ORM was inextricably involved in these changes. It provided the chairman and administrative support to the GMAC Working Group to Assess the Operational Impact of NRSA Stipend and Allowance Changes. The resulting report served as the basis for NIH's implementation plan which was also drafted by ORM. The Grants Management Advisory Committee selected the working group's report as the topic for its first Seminar with the program analyst, ORM, as a co-leader.

The short-term training program for professional students was another important development in fiscal year 1980. ORM participated in the implementation of this program by coordinating the development of the guide for reviewing applications, the modifications necessary in the application instructions, and the development of policies on the start dates and financial provisions under these awards.

ORM was heavily involved with the scientific review of fellowship applications in FY 1980. In addition to regular attendance at IRG meetings, ORM organized three meetings of Scientific Review Branch staff involved with fellowship review to discuss current issues and problems. Such meetings led to review guidelines that should provide more uniformity in the future and a shorter review cycle. ORM also provided preliminary review of fellowship summary statements.

The quality of fellowship summary statements has improved. This sentiment was voiced by a number of the BID's at their secondary fellowship review meetings. ORM coordinated DRG attendance at the BID secondary review meetings and this proved to be a fruitful exchange for both parties.

Revising applications and related forms and brochures appears to be a continuous activity for ORM. In fiscal year1980,most of the revised fellowship forms (PHS 416 series) were finalized, printed, and distributed. The revised forms include the Activation Notice, Termination Notice, and most notably the competing application. Revised program announcements for both NRSA institutional grants and individual awards were also developed. Currently underway in this area is the development of an addendum to the revised PHS 398 form for RCDA's and a revision of the July 1, 1976, NRSA policy brochure.

ORM again is coordinating the compilation of annual training statistics for the National Academy of Science to be used in their training report on personnel needs. Also during the year, ORM developed a report on NIH support of Black Colleges during fiscal year 1979. This government-wide report is coordinated by the Federal Interagency Committee on Education.

The ORM program analyst attended the spring conference on NIH Grants Administration at the University of Maryland at Baltimore; was a presenter at two STEP forums on changes in application forms; and served on the payback guideline committee chaired by Dr. Arthur Hemming.

ADMINISTRATIVE BRANCH

The Administrative Branch continued to provide the Division with administrative and financial management (including budget, and scientific evaluation grants), property and supply control, space planning and assignment; to maintain supplies of publications and application forms used in the PHS extramural programs; and to be responsible for the efficient running of the components for effective coordination of procedures and services, and to maintain procedures for centralized distribution of application forms by the grantee institutions. A number of studies were conducted and/or directed by the Branch involving several management activities, the results of which may mean a reorganization or the application of new technology within the Division.

Financial Management Section: The Section assisted in administering about $16.5 million for the Division's operations, of which $14 million was from the NIH Management Fund, supplemented by $2.5 million from the institutes for the support of the Scientific Review and Evaluation Grants (SREG) awarded to initial review group chairmen. The Section monitored expenditures from these funds through a computer data base system that also provides NIH management with up-to-date monthly cost analyses progress reports. Consultant costs were again paid almost entirely from the SREG's, with consequent savings in both time and effort. The Section continues to report approximately 7,000 individual payments made to about 2,500 consultants who submitted 6,000 vouchers to the NIH-wide computer-based system for reporting consultants' incomes. In addition to the audit of the 6,000 consultants' vouchers, about 1,000 vouchers were audited by this Section for Division employees and others.

The Section prepared the Preliminary Estimate to HHS, the OMB Submission, and the Zero Base Submission for the fiscal year 1981 President's Budget in addition to furnishing information for the fiscal year 1980 Mid-Year Review. Work has been started on the fiscal year 1982 Forward Plan. The Section continues to monitor the orderly flow of obligations and other aspects of budget execution as well as responding to requests from the Division of Financial Management.

Office Services Section: The Section continued to review and approve requests for supplies and equipment needed by the Division; to provide property and supply control, and to participate in space planning and assignment. The Section accomplished a number of physical moves including setting up a pilot work group consisting of six review groups, a word processing center and a central processing center (including a Microfiche camera and duplicator). The Section has also maintained the Division's mail room, and has been responsible for wide distribution of PHS and NIH extramural forms and publications. The Section continued to maintain liaison with other NIH service components for effective coordination of procedures and services; and to be responsible for supplying the control offices of the grantee institutions with application kits.

In addition a major move was made to consolidate most of the Statistics and Analysis Branch offices on the first floor, thereby improving communications and work flow.

The number of grant application kits assembled and handled averaged around 10,000 a month, and about 9,500 miscellaneous packages were mailed each month. The Mail Unit received and processed approximately 35,000 grant applications of all types, and a large volume of supporting documents, letters, and publications.

Extensive technical contributions were made by staff in the development of several new and revised forms, including the new PHS 398 (research grant application form).

The DRG Reference Room, which had been in operation for 20 years, had to be disbanded because of space and staff limitations. The reference material has been decentralized into two basic locations, one housing subject reference texts and the other major reference books such as Index Medicus and American Men of Science. A Reference Committee was formed by the Director to insure the adequate provision of appropriate medical reference materials, but the lack of a centralized facility is a major inconvenience to the staff.

REFERRAL BRANCH

At the time this report was prepared, processing for the January 1981 councils had not been completed. As of August 1, 1980, the Referral Branch had processed and assigned 25,559 competing applications during fiscal year 1980 with an estimated final total of 25,859. In addition, the Branch will have processed 18,363 noncompeting continuation applications by September 30, 1980. The Branch also has processed 2,229 interim supplements as of August 1, 1980.

Staff Activities

The staff participated in a number of activities during the year under review.

The Branch Chief represented the NIH at a Federal Agency seminar held at Louisiana State University in Baton Rouge on March 4 and 5. The Assistant Chief served on the STEP committee and assisted in presenting the STEP forums. He also served on the Awards and Recognition Committee (DRG).

Two employees attended formal training courses entitled, "The Troubled Employee" and "Supervisor's Role in Adverse Actions and Grievances." Other courses attended included "Time Management", and "Effective Supervision." Two employees have been participating in the Upward Mobility Program.

Branch Publications

The Branch has produced a publication entitled, Referral Branch--Functions, which describes the functions of the Branch and how they are carried out. It has been distributed to DRG and to the BID Referral Office contacts.

The Branch is engaged in updating the referral guidelines for study sections and PHS awarding organizations and hopes to have the revised guidelines in print in the near future as part of a Handbook for Referral Officers.

Print Shop Committee

A committee was formed under the chairmanship of the Branch Chief to establish procedures for improving the requisitioning and receipt of duplicated grant applications and summary statements from the NIH print shop. Together with the print shop, the committee designed a procedure which appears to have improved the timeliness of receiving duplicated applications and summary statements.

APPLICATIONS PROCESSED BY THE REFERRAL BRANCH IN FISCAL YEAR 1980

Council		May 1980	October 1980	January 1981
RECEIPT DATE		Oct-Nov 1979	Feb-March 1980	Jun-July 1980
			COMPETING	
Number of Applications (1)	New	7793	6767	
	Renewal	2205	1651	
	Supplement	228	171	
	TOTAL	10,226	8589	6744 (7044)
Distribution (percent)	NIH	75.4	79.3	
	ADAMHA	21.3	16.3	
	Other (2)	3.3	3.9	
			NONCOMPETING	
Type 5		7611	6541	4211[2]
Interim		418	1028	783 [1]
(Administrative)	TOTAL	8029	7569	4994

[1] Through August 1, 1980
[2] Through September 30, 1980
( )Estimated

(1) Includes applications for regular research, program projects, centers, construction, training, fellowships, career awards, and minority programs.

(2) Includes FDA, HRA, OH

RESEARCH ANALYSIS AND EVALUATION BRANCH

Activities in the Research Analysis and Evaluation Branch were concerned mainly with central NIH data resources in the area of Clinical Trials; long term trend data about principal investigators on research grants; analyses and studies to provide a broad overview of selected problems and issues, and solving problems relating to various NIH reporting requirements.

The annual NIH Inventory of Clinical Trials was modified to reduce the reporting load, and efforts were made to bring the Inventory more up-to-date. For Fiscal Years 1977 and 1978, summary statistical tables characterizing the aggregate of all trials by Institute, by support mechanisms, and by experimental design elements were prepared. Individual data sheets were prepared for each trial supported in those two years. A new survey instrument was adopted and used to collect data from the Institutes on Clinical Trials active in FY 1979.

Trend data about new Principal Investigators (P.I.'s) - their rates of entry as P.I.'s on research grants, retention in NIH research grant support systems, and rates of attrition for cohorts of new P.I.'s over more than two decades - were generated to assist in understanding the dynamics of the research manpower pool. The continued decline in the rate of application for research grant support by M.D. applicants was studied. A similar trend was noted for persons with M.D. degrees supported by NIH research training programs. The new P.I. studies did show, however, continued opportunity to obtain research grant support on new research project grants, a majority of which are awarded annually to new P.I.'s.

A variety of subject matter searches and analyses of selected areas of biomedical research was conducted by the Branch, often in cooperation with the Research Documentation Section. A new capability for searching the disease and other subject matter content of research grant application project titles, whether the project was funded or not funded, was developed. The traditional chemistry component (other than biochemistry) was further classified into major subcategories at the request of the Chemistry Division of the National Science Foundation. Some of the subject matter areas studied were the following: health services research, human growth hormone, orthopedic research, prostaglandins, artificial organs, biomedical engineering, radiation research, and urology.

The problem of reporting NIH research programs to OMB and to NSF by the broad classifications of basic or applied research or development was examined by the Branch in order to develop possible alternatives to the present burdensome methods being used. One of the principal objectives of the study in progress is to devise an automated system of reporting that would be relatively stable (for trends) and acceptable to the Institutes and to recipients of these required annual reports.

SCIENTIFIC REVIEW BRANCH

In last year's report, the problems of the heavy workload, inadequate space, and outmoded equipment were stressed. The workload continues to be heavy; during fiscal year 1980, 18,283 applications were assigned to the Scientific Review Branch for review for scientific merit. But the overall situation has improved as a result of several management decisions. Chartered study sections no longer review applications for individual (F32) fellowships or responses to RFAs, and executive secretaries have been encouraged to use other means, such as establishing ad hoc review groups, to relieve the burden on individual reviewers.

With respect to the space and equipment predicaments, the Branch has developed a Central Service Unit, including a Paper Processing Center, a Microfiche Center, and a Word Processing Center. In addition a model space-saving study section office was created. These projects are designed to utilize the most up-to-date and efficient equipment as well as to centralize much of the flow and processing of paper through the Branch. Although these projects are presently operational, they are still in only a preliminary stage of development. It is expected that current plans will be modified and efforts expanded during the next fiscal year.

In addition to the above administrative developments, several documents or materials were prepared. The Handbook for Grants Assistants and Handbook for Executive Secretaries were updated and extensively revised. Also printed was the Orientation Handbook for Members of Scientific Review Groups, which is a modified version of a document prepared by the NIH committee responsible for implementing GPRST Recommendation No. 38. Finally, an extensive, ongoing slide collection of the peer review process was developed for use in lectures or seminars.

A series of forums with institute directors provided the opportunity for a valuable information exchange between the executive secretaries and those individuals operating at the highest level at the NIH. These meetings were well attended and well received.

The Branch was also actively connected with a series of four meetings, held at NIH in the late fall of 1979, involving the chairpersons of all the NIH scientific review groups and key representatives of the NIH administration. The Office of the Associate Director for Scientific Review prepared the Proceedings of the meetings. In Proceedings of the 1979 Meetings of the Chairpersons of NIH Scientific Review Groups, the discussions by the groups and the presentations by Drs. Fredrickson and Raub were merged into a single compact volume. The meetings were highly productive, and NIH plans to continue such forums in the future.

During the June 1980 cycle of study section meetings, the Branch field tested an electronic voting machine with five fellowship panels. The purpose of this pilot test was to provide these review groups with instant feedback on priority scores and the distribution patterns of individual votes. After viewing this information, the group, if dissatisfied, could reopen discussion and revote.

The successful operation of the machine would also eliminate the need for calculating priority scores. One major stimulus for having this pilot test was GPRST Recommendation No. 61, which was accepted by the Office of the Director, NIH: "NIH should conduct studies of the effects on the review process of displaying the raw priority score to the Initial Review Group members immediately after they assign their individual scientific merit ratings, and of giving them the option, at that point, to reopen discussion and rerate the application."

The test was successful and well-received by both reviewers and NIH staff. However, some problems surfaced because the numbering systems on the individual dials did not match the NIH priority rating system. Since the concept of an electronic voting machine has considerable merit, if the existing machine can be modified, it will be further field tested on several study sections reviewing research grant applications. A report is now being prepared by the Office of the Associate Director for Scientific Review.

In the next fiscal year, the Branch will continue its efforts towards ameliorating the workload, space, and equipment problems. In addition high priority items include developing training programs for employees and strengthening the management of the Branch.

Workshops or Symposiums Sponsored by Study Sections

The Endocrinology Study Section sponsored a workshop on Cell Biology and Endocrinology in San Diego, California, on March 20 and March 21, 1980. The workshop, which was chaired by Dr. Gordon Gill, had seven speakers and was attended by approximately 50 to 75 scientists in addition to the members of the Study Section. Its purpose was to inform the Study Section members of the current status of studies in endocrinology using the techniques of cell biology. The problems of hormone action, hormone effects on growth, development, and differentiated function were discussed. A wide-ranging review of the subject also included the use of cell biology to study endocrine effects on cell aging and cancer. The Study Section members discussed the information in depth and concluded that the concepts and information presented broadened their knowledge of the area and gave an accurate perception of the important areas of study and techniques used in the field.

The proceedings of a workshop sponsored last year by the Primate Research Centers Advisory Committee, the Oregon Regional Primate Research Center, and the Nutrition Study Section were published in 1979 under the title of Primates in Nutritional Research. The editor is Dr. K. C. Hayes, Department of Nutrition, Harvard School of Public Health, and the New England Regional Primate Research Center.

The Pathology A Study Section sponsored a workshop in Chantilly, Virginia, on October 22, 1979, on the role of oxygen-derived free radicals in tissue damage. There were 11 speakers and 100 attenders who engaged in active discussions of the interdisciplinary aspects of this rapidly advancing field. Several organ systems and disease states were reviewed from the perspectives of oxygen-derived toxicity and protection therefrom. Interest was expressed in terms of basic biology, carcinogenesis, inflammation, atherosclerosis, and pulmonary pathology.

The Reproductive Biology Study Section sponsored a workshop on "Immunological Aspects of Infertility and Fertility Regulation" at St. Louis, Missouri, on October 22-23, 1979. The purpose of the workshop was to review basic mechanisms involved in the immune response in general, and specifically with respect to the male and female reproductive system including the immunological relationship between mother and fetus; to provide recently elaborated data on antigens of spermatozoa, oocytes, trophoblasts, and early embryos; to review the present status of diagnostic measures of clinical immunological infertility; and to critically evaluate developments in the area of possible fertility regulation by immunological means. From the presentation of the 11 speakers and the discussions involving members of the Reproductive Biology Study Section and approximately 120 scientists who participated in the workshop, it emerged that we are just beginning to understand the unique relationship between the immune system and the female and male reproductive systems of mammals. Also much work needs to be done to understand more fully mechanisms that prevent and promote immunological interferences of processes involved in reproduction. The proceedings of the workshop will be published by Elsevier North Holland, Inc., New York, NY.

Professional Activities

Besides attending Executive Management courses, STEP seminars, and other training and development workshops or courses, staff members presented the following papers, lectures, or seminars:

Dr. Dharam S. Dhindsa, Executive Secretary, Reproductive Biology Study Section, presented a seminar at the Fifth Annual Meeting of the American Society of Andrology held in Chicago, Illinois, from March 11-14, 1980. The subject was the review of research applications by the NIH. On April 4, 1980, Dr. Dhindsa gave a seminar on "The Influence of the Number of Embryos in Maintenance of Pregnancy in the Pig" at the Laboratory of Human Reproduction and Reproductive Biology, Harvard Medical School, Boston, Massachusetts.

During the fall of 1979, Dr. Martin Frank, Executive Secretary, Physiology Study Section, participated in a course entitled "Cell Biophysics" presented to graduate students in the Department of Physiology, George Washington University School of Medicine. Dr. Frank also participated in a seminar on "Research Funding: Policies and Mechanisms: NIH and NSF" presented to the Department of Physiology, George Washington University School of Medicine, on May 6, 1980.

In December 1979, Dr. Milton Gordon, Executive Secretary, Bacteriology and Mycology Study Section, assisted in the organization of and participated as a group leader in an ESRAC-sponsored workshop on Conflict of Interest. Dr. Gordon served as a group discussant at a Minority Biomedical Support Program Workshop in March 1980.

The professional activities of Dr. Miriam Kelty, Executive Secretary, Human Development Study Section, are as follows. From October 1979 to June 1980, Dr. Kelty has been an invited participant in the Washington Area Bioethics Seminar, an ongoing seminar with participants from area academic institutions, government agencies, congressional committees, public interest groups, the religious community, and the journalist community. The seminar meets monthly to discuss ethical issues in science and technology and their implications for society. On April 17-19, 1980, Dr. Kelty participated in the regional meeting of the Society for Research in Child Development. Dr. Kelty participated in a training program jointly sponsored by NINCDS, Johns Hopkins, and the Academy of Behavioral Medicine on Behavioral Bases of Neurology on April 24-25, 1980. On May 5-7, 1980, Dr. Kelty represented NIH at a research development meeting attended by representatives of more than 50 universities and colleges in Illinois, Iowa, and Mississippi. In addition, she met with Institutional Review Board members to discuss policies and procedures when reviewing research from an ethical standpoint. Dr. Kelty, on May 12-13, 1980, was an invited participant in the American Family Forum, one of a series of workshops on socially important issues sponsored by General Mills to bring together academicians, government officials, and representatives of the public interest to deal with utilization of research and population survey data for policy planning. On June 11, 1980, Dr. Kelty was invited by the Director, National Institute for the Handicapped, to speak to staff and consultants on future developments in the next decade that may impact on the handicapped. During the July 20-25, 1980, meeting of the International Congress of the World Future Society, Toronto, Canada, Dr. Kelty was the United States organizer of a 21 session module. Dr. Kelty organized the health and medicine program, chaired two sessions, presented a paper on ethical aspects of the technological advances in health and medicine, and reported on the program to the plenary session. On September 1-5, 1980, at the American Psychological Association annual meeting, Dr. Kelty delivered the Presidential Address to the Division of Psychologists in Public Service, chaired the Executive Committee and Business Meeting of that Division, and presented awards. As Past-President of the Division of Population and Environmental Psychology, Dr. Kelty was involved in the scientific program, Executive Committee, and business meetings and in chairing sessions. As chairwoman of the Public Affairs Committee of the Division of Health Psychology, Dr. Kelty has been instrumental in initiating a new scientific journal, and has served as liaison with other societies and in governance of the parent organization. As a Fellow of the Division, Dr. Kelty served on the Fellowship Committee to elect new Fellows.

Dr. Samuel C. Rawlings, Executive Secretary, Behavioral Sciences Study Section, and Terry J. Yates presented a paper entitled "Visual Evoked Potentials From High-Density Checkerboard Depth-Reversed Stereograms" for the annual meeting of the Association for Research in Vision and Ophthalmology in May 1979. Drs. Rawlings, Marsh, and Mumma gave "Evaluation of Clinical Stereoacuity Tests" at the annual meeting of the American Academy of Ophthalmology in November 1979.

Dr. David J. Remondini, Executive Secretary, Genetics Study Section, presented a seminar on "Your Grant Proposal: What Happens to it at NIH" on September 27, 1979. This seminar took place at the University of California, San Francisco.

On October 24-26, Dr. Michael E. Rogers, Executive Secretary, Bio-Organic and Natural Products Chemistry Review Group, was Chairman at the Medicinal Chemistry Section, Southeastern Regional American Chemical Society Meeting at Roanoke, Virginia.

On September 28, 1979, Dr. Thomas M. Tarpley, Executive Secretary, Oral Biology and Medicine Study Section, spoke on "Extramural Trends and Peer Review at the National Institutes of Health" at the State University of New York in Buffalo. Dr. Tarpley gave a talk on "Peer Review and Funding Possibilities at the National Institutes of Health" at the University of Maryland Dental School on December 14, 1979. On January 15, 1980, Dr. Tarpley presented a short course on "Non-Neoplastic Salivary Gland Lesions" for the U.S. Navy, Bethesda, Maryland. The next day, Dr. Tarpley spoke on "Salivary Glands - Lumps and Bumps" to the Uniformed Services Medical School, Bethesda, Maryland. "Salivary Gland Disease," the 27th Annual Course in Oral Pathology was given by Dr. Tarpley to the Armed Forces Institute of Pathology, Washington, D.C. on March 7, 1980. On March 20, 1980, Dr. Tarpley gave a 2-hour seminar to Navy residents. On April 9, 1980, Dr. Tarpley gave a graduate seminar at the Georgetown University School of Dentistry on "Salivary Gland Review." Dr. Tarpley was a guest speaker for the Boston Section of the AADR on April 29, 1980. On May 23, 1980, Dr. Tarpley gave a U.S. Army Institute of Dental Research graduate seminar entitled "Sjögrens Revisited" at the Walter Reed Medical Center, Washington, D.C.

Dr. Adolphus Toliver, Executive Secretary, Biochemistry Study Section, spoke on the NIH peer review system and on grantsmanship at the following institutions: Department of Biochemistry, School of Medicine, Baylor University, Houston, Texas (February 15, 1978); Department of Biochemistry, Atlanta University Center, Atlanta, Georgia (June 1978); Emory University School of Medicine, Atlanta, Georgia (August 4, 1978, and August 14, 1979); the University of New Mexico, Albuquerque, New Mexico (August 31, 1978); Bruce Lyon's Memorial Laboratory, Children's Hospital Center of Oakland, Oakland, California (February 1979); Rocky Mountain Branch of the Society of Research Administrators, Denver, Colorado (April 4-6, 1979); Department of Biology, Jackson State College, Jackson, Mississippi (June 6, 1979); Tuskeegee Institute, Tuskeegee, Alabama (September 17-18, 1979); Clemson University, Clemson, South Carolina (November 1979); Department of Anatomy, Howard University School of Medicine, Washington, D.C. (January 9, 1980), and Division of Genetics and Molecular Medicine, Meharry Medical School (January 16, 1980). Dr. Toliver was Chairman of the Biochemistry Sessions, Seventh and Eighth Annual Minority Biomedical Support Symposia, Atlanta, Georgia, on April 15-18, 1979, and April 7-8, 1980. On August 6, 1980, Dr. Toliver became a member of the American Society of Biological Chemists' Committee on Equal Opportunities for Minorities.

On November 27, 1979, Dr. Harold Waters, Executive Secretary, Pathology A Study Section, participated in a workshop on NIH grantsmanship and mechanisms of support at Ohio University, Athens, Ohio. Dr. Waters gave a seminar at the Harvard Medical School on "The Health and Disease of NIH Research Proposals" on January 21, 1980.

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STATISTICS AND ANALYSIS BRANCH

The Statistics and Analysis Branch (SAB) is involved in almost every facet of NIH's extramural activities. Through its IMPAC System (a central data system on extramural activities), the Branch performs services at virtually every stage of application processing, from initial receipt through the final award. SAB assists the Referral Branch by providing every 2 weeks a microfilm containing information on all applications, awards, and contracts recorded in the system, and the Scientific Review Branch by providing various documents, such as the resume of IRG Actions and the Application Summary Statement (Pink Sheet). SAB also assists the national advisory councils, as well as the awarding units, by providing such services and documents as the resume of Council Actions and the Notice of Award with accompanying Approval List.

While providing these services, the Branch is at the same time developing a data base on the extramural activities of the NIH. This data is used to support all levels of NIH management and to provide a source from which NIH can meet its reporting obligations.

SAB also operates a sophisticated computer disk storage and retrieval system, CRISP. CRISP (Computer Retrieval of Information on Scientific Projects) maintains scientific information, under approximately 7,900 subject headings, on all PHS-supported research projects by fiscal year back to fiscal year 1971. CRISP generates annually the 2-volume Research Awards Index that lists the research projects supported by the Public Health Service during a given fiscal year. Volume I provides a fully cross-referenced subject index of currently supported research. Volume II lists (1) project identification data (which include project number, title, and name and address of principal investigator), (2) a separate contract section, and (3) a final section listing project investigators alphabetically, followed by their associated project numbers.

Through its two major information systems, IMPAC and CRISP, and other smaller systems, SAB provides information services on extramural programs to all levels of management, other Government agencies, and the public at large.

1. Office of Systems Planning

The Office of Systems Planning continued its efforts to improve the IMPAC System and to expand services to its users. In addition to new systems and systems modifications described below within the various reports of the individual sections of the Branch, the Office expended major efforts on the following:

Specifications were writtern and the programming begun for a system which will permit the institutes to produce award statements at computer terminals. Persons with a minimum of computer experience, using an interactive program, will be able to edit and update the IMPAC record before the final printing takes place. In addition to the Award Statement all mailing labels will be produced and the program will trigger the printing of the encumbrance lists.

The Award Statement form itself has been redesigned so that four mailing labels can be printed immediately following the printing of each award. In an effort to reduce costs of handling and sorting, the new forms will be used under the present centralized procedure as soon as they arrive from the printers.

As a result of a study done last year, a word processing prototype service unit was established in the Scientific Review Branch. The unit is capable of handling the typing needs of 20 study sections and will eventually be expanded to accommodate all study sections. The grants clerks received basic training in the use of the equipment and plans have been made for further training. The programming effort required to link the word processor to the computer via 1600 bpi tapes is underway and we should be able to produce microfiche from the COM unit in the near future.

During the year the file containing approved multi-project applications has been expanded. The subproject system is being analyzed and procedures are being established to produce an Addendum to the Notice of Award providing a detailed listing of subprojects being funded. Implementation is expected to begin with fiscal year 1981.

In June 1980, procedures for processing the Personal Data page of the new Grant Application Form, PHS 398, were established. Three personal data items on Principal Investigator/Program Director: date of birth, sex, and racial/ethnic origin will be entered in the IMPAC files and stored encoded. The data can be retrieved only by special decoding techniques for aggregate statistical determinations.

Proposed procedures for processing applications under joint-funded programs were prepared. The decision was made to postpone joint-funding of Short Term Research Training awards, and, therefore, procedures were not implemented. Nonetheless, programming for a special Joint Funding file in IMPAC is continuing in preparation for future implementation of joint-funded applications and awards.

During the course of a GAO audit of NIH research contracts, it was found that no information was maintained in the IMPAC system on the date that a contract obligation was incurred. In light of this fact, a new data item was established indicating the date the contracting officer signed a contract action.

In response to a request from the Division of Contracts and Grants, DRG established a new data item (Item 196) for research contracts indicating whether or not a Departmental audit had been requested on a contract that had expired. Data for this item is supplied by the DCG.

New procedures were established to track applications involving ionizing radiation through the NIH review process. After study section review, the executive secretaries provide a listing to the Chief of the Referral Branch of all applications involving ionizing radiation. The list is forwarded to the Statistics and Analysis Branch for updating the IMPAC system. A new IMPAC report was established to provide detailed information to Director's office. This procedure is to be instituted for the applications assigned to the January 1981 review cycle.

2. Data Processing Section

The Data Processing Section continued its efforts to improve the quality of service to the BIDs and to streamline and improve internal data processing and computer operations. Discussion of some of the major new efforts undertaken during the year follow:

A report module was programmed this year to provide study section staff with the facility to order a series of special labels and reports during the initial review phase of application processing. Study section staffs can initiate requests through WYLBUR from remote stations or through DPS channels. The reports and labels were designed to aid study sections in setting up file folders, in mass mailing, and in creating lists of applicants sorted by name, organization, and so on.

A Query via an Interactive Communications (QIC) program was designed for the NIH Committee Management Information System (CMIS) data base. The CMIS contains current and historical information pertaining to the establishment of chartered public advisory committees and the appointment of their members. The new query program provides ready access to the membership file by member's name, area of expertise, committee name, termination date, gender, or organizational location.

The PHS Contract Information System requires that NIH transmit monthly data on active research contracts in the form of a computer magnetic tape and listing. All IMPAC research contract records are examined to determine if the contract is or was active during the current fiscal year. If active, the base record and all modifications are selected and forwarded to the PHS CIS.

The computer prepared Institute Action Form, used by the BIDs to initiate an award from IMPAC, has been combined with the ICMS worksheet into one form, a Grants Management Worksheet. This form will be computer prepared and sent to the BIDs for completion. Upon completion, the BID will file one copy in the official folder, send one copy to DPS to use in preparing an award, and one copy, as necessary, to DFM to compute indirect cost.

3. Research Documentation Section (RDS). The Section maintains a computerized disk storage and retrieval system, CRISP (Computer Retrieval of Information on Scientific Projects), containing scientific data on research grants and contracts supported by the Public Health Service, and NIH and NIMH intramural research projects. Through this medium, RDS responds to ad hoc and recurring requests for scientific information from Government administrators, scientists, and information personnel for purposes such as analysis and evaluation of research programs, specific scientific areas, and preparation of reports. Similarly, the Section responds to inquiries from grantee and nongrantee institutions and scientists, the news media, and other non-Government sources engaged in, concerned with, or reporting on medical research.

RDS publishes annually as a "spin off" of the CRISP file:

1) The Research Awards Index prepared in two volumes. Volume I is a scientific subject index with associated project numbers and titles. Volume II contains three sections: (a) project identification data, (b) research contract identification data, and (c) project investigator information.

2) The Medical and Health Related Sciences Thesaurus, the vocabulary authority list of subject headings used by the RDS indexing staff in indexing research projects.

CRISP has the query capability of (a) providing, in several optional formats, information ranging from a straightforward listing of research pertaining to a single scientific subject term to a compendium of projects relating to any number of terms, using a combination of Boolean search logic: (b) furnishing individual institutes with tapes or hard copy of their projects by subject, project (subproject), title or name of investigator, and (c) generating institution/institute listings of projects with indexing terms (Scientific Profiles). CRISP also has the query capability to limit subject searches or Scientific Profiles to certain program (R, M, N, P, S,Z) or IPF codes.

A specially designed CRISP subroutine can supply grantee institutions or NIH institutes possessing appropriate computer capabilities with specially formatted tapes which they can use to search the scientific subject content of their own research grant and contract records. This subroutine called CESI (CRISP Extract System for Institutions/Institutes) is updated monthly and can furnish select tapes on an ad hoc or recurring basis.

Subproject Information. A significant feature of the CRISP system is its capability of subdividing program projects, center, and other large projects into their individual research components thereby providing more detailed and accurate information of the research objectives of these large grants, in addition to the names of principal investigators conducting the research.

CRISP Services. During fiscal year 1980, the Section responded directly to over 1000 requests on a wide range of subjects; prepared videocomp tapes used in the creation of extract Indexes and related material for nine institutes; provided Scientific Profile data reports and/or CESI tapes for grantee institutions; furnished NIH-wide scientific area data for appropriate institutes; and performed professional editing operations involving thousands of approved research grant and contract applications. In addition, the Section played a significant role in providing material on various trans-NIH issues such as diabetes, arthritis, genetics, nutrition, hematology, gastrointestinal diseases, cystic fibrosis, pregnancy, behavioral sciences, health care, and nephrology.

Intramural Research Projects. Professional indexing and entry into CRISP of scientific keyword, title and principal investigator data from fiscal year 1979 intramural research projects were completed soon after receipt of the last annual report in March. This information was subsequently published in the annual NIH-NIMH Intramural Research Index.

Research Awards Index. (NIH Publication NO. 80-200). Published in the spring, the Index features a new cover, and a leaner look. Limiting its subject section to the primary objectives of each research project has resulted in page volume reduction to about one-half that of the 1978 edition.

On-line access. A number of NIH institutes directly access CRISP file 5 which contains project narratives for PHS grants and NIH contracts, as well as intramural research conducted by NIH and NIMH. Information from this component of CRISP is also furnished in hard copy format to several other institutes. In addition, some institutes also iterate CRISP subject files on-line. It is requested that RDS be contacted before running subject searches to assure that optimal results are achieved.

Improvements in Data Processing Activities. During the current calendar year, a task group has been established for development of more efficient data processing and filing procedures within the Section's Processing and Publications Unit. The initial efforts were directed toward reducing file volume as well as improved and more reliable methods of document receipt, coordination and control. Although all benefits have not yet been fully realized, a significant improvement in work area utilization has already been achieved. The second objective centers on the development of programs employing interactive and TSO routines for assuring greater accuracy and faster turn-around time in data capture and associated operations.

4. Reports, Analysis, and Presentations Section

The primary function of the Section is to satisfy the information requirements of NIH and PHS centralized extramural activities. In fulfulling this function, the Section utilizes the IMPAC system, as well as other data sources. Its responsibilities include: design, maintenance, and operation of computer reporting systems; training and technical assistance in data retrieval; planning and coordination of NIH responses to annual surveys covering Federal obligations for research and development;preparation of formal publications such as listings of NIH grants and awards and the NIH Basic Data Booklet; statistical analysis to compile and present visual materials dealing with extramural trends or other topics; and the development and implementation of special evaluation projects. This Section also works closely with the Data Processing Section in maintaining and extending the IMPAC system, and has direct responsibility for establishing institution classifications and related computer files, as well as ensuring the accuracy of selected key data items for publication or reports.

Extramural Information Services

Approximately 19,500 queries were processed by the Section during fiscal year 1980, primarily in response to requests for information from NIH officials, other government agencies and nongovernment organizations. These queries utilized all data capabilities of the NIH IMPAC system; many required compilations of historical data, designing special reporting files, providing consultation services, and developing specifications to ensure that requesters' needs were met. The bulk of the queries produced hard copy listings, but the Section also supplied large numbers of magnetic tapes, which were used by requesters directly to answer questions, or which were entered into other management information systems.

About 175 different reports on currently active or fiscal year awards to date were prepared on regular monthly, quarterly, or annual schedules for extramural program managers and administrators. The data in these reports were organized by geographic location, principal investigator, program class, grant number, budget start date, and other relevant variables. An additional 79 reports were prepared for the institutes and divisions before each round of national advisory council meetings, showing detail on competing grant applications. A total of 27 different computer tape transmittals were provided to a majority of NIH Institutes on regular weekly, monthly, and annual schedules. Listings and address labels were furnished to DFM, ADAMHA, HRA, and FDA on a monthly basis, identifying grants for which reports on expenditures were overdue. The Section compiled a number of tables for each quarterly issue of the NIH Management Data Book. Statistical summaries of initial review group actions on competing research and training grant applications were prepared during each review cycle, as in previous years. Beginning with the May 1980 council review cycle, a new series of recurring reports was developed to provide additional information on competing applications reviewed and recommended for approval, together with various statistical measures of priority score distributions such as means, medians, standard deviations, and lowest and highest scores for each study section. These reports were designed to provide information enabling Institutes to evaluate and use actual priority scores for decisions formerly based on normalized priority scores which, after fiscal year 1980, will no longer be available in the IMPAC system. The Section also served as the authoritative source for information on the workload of DRG study sections. Several weeks after the cutoff dates for receipt of applications for review cycles, statistical tabulations were prepared showing the volume of applications to be reviewed by each study section, by institute and type of grant or activity; and for primary and secondary institutes, amended applications and dollar values of applications requested. Following the completion of each review cycle, special summaries of DRG study section actions were provided to assist in managing and monitoring their review activities.

As of June 1980, 30 institutions were participating in the NIH/Grantee Institution Interface system. This system provides an institution with information on its awards and pending applications in standard hard copy formats, magnetic tapes or microfiche in exchange for feedback from the institution to NIH concerning the accuracy of the information.

A series of tabulations of research and development contracts were provided to DCG/OD quarterly, semi-annually, and annually for inclusion in reports to the DHHS, showing data by institute or division, type of contractor, type of contract, competitive versus noncompetitive contracts, and dollar-award intervals.

A series of reports on NIH training activities was prepared for the National Academy of Sciences, as in previous years. These reports consisted of 24 tables, showing training awards by year, institute, activity, discipline, specialty or field, academic level, and so forth. The Academy was also provided detailed information from each training appointment and fellowship award to update its roster of the individuals supported by NIH training programs.

The Section devoted considerable effort toward completing three annual government-wide surveys of research and development. The National Science Foundation survey entitled "Federal Funds for Research, Development, and Other Scientific Activities" covers all NIH intramural and extramural research activities for the past fiscal year together with the estimated obligations for the next 2 fiscal years, by performer, field of science, geographic area, basic and applied research and development, and combinations of the above. In connection with the responsibilities of the Section for preparing this survey, the Section obtained data from the institutes allocating the amount of basic and applied research and development for each research grant and research & development contract. The annual survey by DHHS of obligations to institutions of higher education and other nonprofit organizations (known also as the CASE report) required summaries of all NIH extramural support, by activity, for individual institutions and health professional schools. The Section also prepared the NIH response to NIH's own annual survey of obligations for medical and health-related research covering intramural and extramural research and development obligations, by field of science, performer, program, and State.

The Section published the annual "Brown Book" series of NIH extramural awards for fiscal year 1979, including separate volumes on research grants; training, construction, cancer control, and medical library grants; and research and development contracts. The Section cooperated with the staff of the Office of the Director, NIH, in compiling data on extramural activities for the annual publication entitled "Basic Data Relating to the National Institutes of Health." Several new tables showing trends in extramural awards were proposed by the Section and incorporated in the 1980 edition. An analytically oriented chart book entitled "NIH Extramural Trends, Fiscal Years 1970-1979" was prepared for internal use. Several sets of 35mm slides were compiled to enable these charts and related materials to be presented to various audiences. The Director, DRG, and the Associate Director for Extramural

Research and Training, NIH, were given their own sets. Additional formal publications of the Section included NIH Fellowship Awards; Fiscal Year 1979; the Statistical Reference Book of International Activities, and the companion volume listing each international award, both issued in cooperation with the Fogarty International Center; and the quarterly compilation of NIH new grants and awards.

During the year, the Section participated in a number of special projects and studies to develop data and projections required for fiscal year 1981 and fiscal year 1980 NIH budgets. These included a variety of reports prepared for DFM covering estimated amounts needed to fund research project applications with priority scores of 250 or better; the volume of research project applications reviewed; estimated applications to be reviewed and approved, eligible for award, awarded, and award rates; distribution of awards by type of institution, average awards per principal investigator, and so forth. Reports were also prepared showing estimated NIH commitments for fiscal years 1981 through 1986, to aid in determining future budget requirements and to ensure consistency and standard presentations of institute projections. Several simulation models, based on varying assumptions concerning NIH competing research project awards were developed to describe when and how NIH could stabilize the number of research projects. The Section also assisted the investigative staff of the House Appropriations Committee in conducting a study of NIH data and estimates concerning numbers of applications and priority score paylines.

To deal with the problems faced by NHLBI and other institutes that have relied on normalized priority scores, the Section undertook two major projects. First, in cooperation with NHLBI, a system was developed for ranking grant applications on a comparable basis, using percentile distributions of actual (raw) priority scores. Second, efforts were initiated to acquire a capability to present information on study section behavior, using advanced techniques of computer graphics. It is planned to produce, before each council meeting, a variety of computer-generated charts that will be designed to facilitate comparisons of priority scores and recommendation rates for the various study sections.

Another project was initiated to identify and resolve the problems of reporting DFM obligation data, as recorded in the IMPAC system. The Division of Financial Management, as a result of this project, can now receive tabulations from the Section which distribute obligation totals reported through official budget and accounting channels into any of the classifications contained in the IMPAC system. It is believed that this capability will facilitate NIH budget analysis and presentation by speeding up the process of obtaining and presenting valid budget data at the end of each year.

The Section worked very closely with the OD/NIH staff responsible for research manpower policies and procedures in developing new discipline, specialty, and field codes to replace those which have become obsolete. This work included the preparation and transmittal of worksheets to the institutes, capturing information from these worksheets as they were returned, developing computerized tables and files to record new codes, and generating reports based on the new codes. This effort, when completed, will enable NIH to have a much more accurate and understandable presentation of its training activities.

Finally, the Section began a series of studies to communicate institution-oriented data more effectively. The first two studies concerned: (1) whether the real dollar growth of extramural grants and contracts during the last 10 years was limited to the same group of institutions that were participating in the programs at the beginning of the period and (2) why there are more institutions of higher education and research institutes and fewer hospitals participating in extramural activities.

Systems Support and Development Activities

The Section has established and maintained the Institution Profile File (IPF) to serve as the central registry of names, locations, geographic and other selected data for organizations participating in the Public Health Service extramural programs. This file assures uniform reporting and eliminates the necessity for storing similar information in individual grant and award files. In fiscal year 1980, approximately 1,000 new institution records were added to the IPF, and there were more than 28,000 item updates. The IPF now contains about 26,000 records on institutions which have participated in NIH or other PHS activities since fiscal year 1938.

During fiscal year 1980 the Section continued to support the PHS Grants Data System (GDS) by supplying monthly magnetic tape extracts of all records contained in the NIH IMPAC system for grant awards, and by supplying IPF codes for institutions newly recorded in the GDS system. This support ensures consistent and accurate PHS-wide reporting on institutions.

The Section continued to develop and maintain an index of major components and departments for institutions of higher education. This system ensures consistent coding of applications and awards in order to identify support to medical schools, surgery departments, and so on. A new edit system was installed to match the index with fiscal year 1980 awards during the year. This system will eliminate the extensive and time-consuming requirement for hand-editing, which has delayed the availability of complete data for previous fiscal years. During fiscal year 1980 approximately 220 new department codes were added to the index, and there were more than 7,000 item updates. The index now contains about 20,000 lines, consisting of about 2,000 institutions of higher education, approximately 16,000 major components and departments, and about 2,000 reference lines for internal use.

As in previous years, this Section was responsible for creating and maintaining a special set of fiscal year 1979 "Publication" files, which serve as authoritative sources of data to determine trends, or year-to-year changes, in the amounts and distributions of NIH extramural awards.

The Section also continued to operate the system of fiscal year reporting files containing data on professional and other positions paid under NIH research grants. These data are based on manpower reports (Form NIH-1749), which were submitted by principal investigators for fiscal years 1973 through 1978 awards. The information available through this system includes occupational categories, number of paid weeks worked, full-time equivalent employment, degrees, sex, age, salaries received from grant funds, and the discipline, specialty or field for project employment. Four reports have been published containing summary statistics on employment under NIH grants awarded in fiscal years 1973 through 1976. These reports focus on employment and salaries by awarding institute; comparisons of training support by research grants, fellowships, and training grants; female employment; and trends in Ph.D. and M.D. personnel. Three of these reports were updated during fiscal year 1980 to include data for grants awarded in fiscal year 1977. Comparable data for fiscal year 1978 grants also became available during the year.

An independent contractor completed an evaluation of the Manpower Report system during fiscal year 1980. Potential improvements in the design of the form and in the procedures for obtaining the forms were studied, together with the uses of these data. This report was used in making the decision to discontinue the Manpower Report after the data for fiscal year 1978 grants are completed.

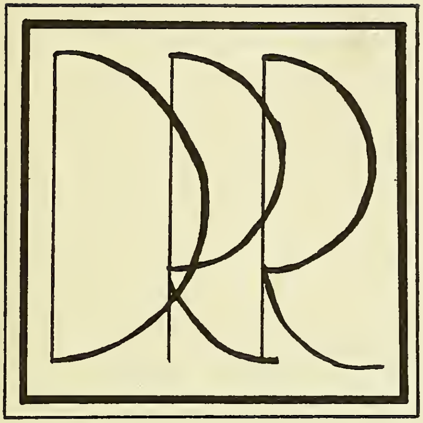
The Section continued work on the Research Grant Expenditure Report system. This computer-based system currently covers NIH research grants for fiscal year 1971 through 1975. During fiscal year 1980, preliminary work was begun to justify and award a contract to enlarge this data base to cover fiscal years 1976 through 1978.

Retrieval Training

The Section has long been responsible for assisting institute staff in developing and applying systems and programming techniques which would facilitate their independent use of the IMPAC system. A senior computer specialist is available and responsible for providing these services on a full-time basis. During the year, two basic and one advanced training course on how to use the Inquiry and Reporting System were offered. A total of 45 persons attended these courses. In addition, there was an average of six personal consultations each day.

Graphic Arts

The Visual Information Specialist finished approximately 2,311 pieces of graphic artwork and photographs. These included work such as charts, tables, certificates, signs, scrolls, flyers, cartoons, drawings, and vugraphs, for publications, presentations, and so on. Most of the work was for OD/NIH and DRG staff; other recipients included staff of the National Institute of Arthritis, Metabolism and Digestive Diseases, and the National Heart, Lung, and Blood Institute. In addition, the Visual Information Specialist coordinated work of a contractor (Creative Technologies, Inc.) as follows: 640 new slides, 104 revised slides, 770 duplicated slides, 62 black and white prints, and 3,000 color xerox copies. The NIH photography lab made approximately 3,000 duplicate copies of the new slides due to the heavy demand for sets of the presentation that these slides represented. The Visual Information Specialist personally finished 273 preliminary drawings and sketches for the creation of slides, in addition to coding the artwork for slides for letter size, color, etc. He also advised or consulted with officials concerning the format, color, composition, and so on of slides. Examples of presentations which he coordinated and helped design cover the IMPAC and CRISP systems, and a library of slides on the grant application process. Other presentations worked on include: "The Influence of the Number and Location of Embryos on Maintenance of Pregnancy in the Pig," RAE/DRG's "Principal Investigators," OD/DRG's "How a Research Grant is Made," and OD/NIH's "Models of Stability." Many of these slides are used outside NIH by other agencies and universities.



DIVISION OF RESEARCH RESOURCES

ANNUAL REPORT

FISCAL YEAR 1980

(October 1, 1979 - September 30, 1980)

National Institutes of Health
Bethesda, Md. 20205

MISSION:

Identifies and meets the research resource needs and opportunities of the NIH by conceiving, creating, developing, and assuring the availability of those resources that are essential for the efficient and effective conduct of human health research.

Helps institutions establish and operate general clinical research centers where research studies can be conducted on patients over a wide range of human diseases; supports highly sophisticated biotechnology resources, such as computer centers, high voltage electron microscopy centers, and biological structure determination centers; supports primate research centers; increases and improves laboratory animal facilities and resources; makes awards for minority biomedical support, and provides institutional research support for stabilizing and developmental efforts among a variety of institutions throughout the United States.

Provides a unified approach to solving the many complex needs of health-oriented research that tends to be institutional, regional, or national in scale.

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REPORT OF THE DIRECTOR

Dr. Thomas G. Bowery

I. Report of the Director

The initial effort during fiscal year (FY) 1979 to develop a multi-year program plan culminated in success during FY 1980 with the actual production and distribution of a 140 page document entitled, Division of Research Resources Five-Year Program Plan, 1982-1986. In this document, DRR has set forth an array of more than 60 actions for research resources judged to be important to sustaining the momentum of biomedical investigations on a broad front of basic and clinical sciences. It is a plan about research needs and opportunities that delves into the pursuit, practice, and productivity of biomedical research by individuals and institutions as impacted by the availability and utility of resources. The architects of the plan have decided upon actions that respond only to the most solid core of the many research resource needs of scientists at extramural grantee institutions. Identified also in the plan are actions that involve policy issues of NIH-wide interest and concern.

In addition to the DRR staff, a number of groups of consultants have participated in the development of the plan over the past year. Throughout the planning period, members of the National Advisory Research Resources Council (NARRC) have been actively involved in program-specific work groups and as a collective body, providing ideas about, and advice on, priorities for actions that were under consideration. Significant contributions to the plan, including initial and continuing debate on issues, options, and opportunities for resources, came from the different program review and advisory committees serving DRR. Meeting on a number of occasions with staff and Council, they provided data, answered staff questions about needs, alternatives and priorities, and compiled panel reports to assist in the drafting of program plans. Other ad hoc consultant groups to the Division gathered and analyzed data and developed option papers for special initiatives. The real sum and substance of the DRR program planning creativity, however, arose, as it must, within the managerial realms of each program--the program directors and their scientific staffs. It was they who synthesized the ideas and drafted the DRR planned actions for new resource initiatives, as well as those future steps for either enlarging, enhancing, or closing down various existing resource activities.

During FY 1980, the working draft of the Five-Year Plan served as the base for the Division's Evaluation and Research Plan Review Session with the Director, NIH. In addition, the Plan served as the policy framework for the budget priorities developed for the President's Revised Budget for FY 1981 and the Division's Preliminary Budget submission for FY 1982.

In addition to contributing to the planning effort, the Office of Administrative Management carried out these important activities--

- Through a series of meetings with NIH and other Federal staff, we helped to explain the potential effects of two legislative proposals--H.R. 7036 (Health Research Act of 1980) and S.988 (Health Sciences Promotion Act of 1979)--on the DRR. While the fate of these two Bills is not now clear, the impact on this Division is now generally constructive.

- The National Academy of Sciences has completed a survey of laboratory animal facilities, transmitting the survey results to us. We in turn have alerted NIH to the need for a major effort in constructing institutional facilities for research animals.

- Extensive effort was devoted to the expansion of the DRR Management Information System. Individual subsystems to provide program-specific data and reports are now available to staffs of the Biotechnology Resources, General Clinical Research Centers, and Minority Biomedical Support Programs. Using these subsystems to analyze active grantees and contractors will help program managers to better understand the interactions between researchers and research resources, and to better plan for new research resources.

  Along with support for program management, much staff time and effort were devoted to the development of computerized capabilities to support the Division's budgeting process. For example, the criteria for a report which provides a forecast of DRR's future years' noncompeting continuation commitments as well as for the known or estimated competing continuation costs for all grant mechanisms and contract mechanisms were defined, using NIH's IMPAC as the data base. Also, the specifications for tables needed during the budget process were developed; those specifications were incorporated into an Autotab table system which is now used by top management in deciding budget increases and decreases.

  A third important area involved collecting and analyzing of all data from the 1979 DRR annual progress reports. The services of the Division of Computer Research and Technology's data conversion unit were used for data entry. Following normal editing processes, the data were made available to DRR Special Projects staff and were used to answer the many NIH scientific inquiries received.

  Finally, the Data Management staff were deeply involved in providing computer simulation support for this year's redesign of the Biomedical Research Support Grant formula allocation. This process, which is described in greater detail later in this report, allowed this Division to develop and recommend to NIH a new allocation formula which will return our distribution to the 1976 pattern.

- Our staff completed the final activities associated with the Government-wide three-year audit of position classifications. These activities have involved a complete investigation and review of all our position descriptions, reclassification of several, and out-placement of a small number of DRR employees into other NIH positions, thereby assuring retention of grades for the individuals. At the same time, the staff were also responsible for implementing the first procedures of the Civil Service Reform Acts; specifically, 18 DRR staff were subject to the provisions of the new Merit Pay System. In order to meet the requirements of this system, these 18 individuals entered into Merit Pay work plans, essentially contracts of work objectives to be accomplished during the year. At the end of the work year, performance appraisals were made for these 18 individuals, and commensurate salary increases were awarded.

- Several individual pieces of expensive office equipment have been leased for the past several years. In some cases, these leases were converted to purchase arrangements, thereby saving the Division several thousand dollars over the next three years.

- To the existing core of automated word processing equipment will be added several stand-alone word processing machines which have additional computer-terminal capability. These additions will be made in FY 1981 based on requirements identified at that time and a 1980-completed cost comparison study.

Other major activities within the Office of the Director centered in the Office of Science and Health Reports.

The Research Resources Information Center (RRIC) continued to expand its services and coverage of DRR activities during FY 1980.

The Office of Science and Health Reports established the Center in 1976 and has offered project and technical guidance since that time. The objective of the RRIC is to promote the awareness of, the value of, the utilization of, and the access to DRR-supported research resources.

The impact of the RRIC on the scientific community is evinced by the increased number of phone calls and requests from investigators and administrators in the field concerning the Center's services. Included were the dramatic increase in requests to be put on the Research Resources Reporter mailing list, requests for publication of notices in the Reporter, suggestions by DRR grantees for articles on new research developments, the assistance of a DRR resource on the filming of a new biotechnology process, response to the new OSHR-suggested "Research Services" section of the Reporter, and unsolicited comments by various scientists, educators, and administrators regarding the use of Reporter articles for actual lecture hall presentations.

The circulation of the Reporter has increased from 14,000 monthly at the end of FY 1979 to 17,000 at the end of FY 1980. Individual requests to be added to the mailing list now average 800 every three months. There are now 16 Reporter newsstands distributed at the NIH campus and associated NIH office buildings in Bethesda and at GCRCs in San Diego, San Francisco, and Torrence, California.

In addition to the monthly issuance of the 16-page Reporter, the RRIC completed the research, writing, and editing, with OSHR assistance, of two major special reports during the year. "The Seeds of Artificial Intelligence: SUMEX-AIM," a 74-page publication, containing 42 photos, charts and illustrations, was produced in March 1980; and the 32-page "Division of Research Resources 1979 Program Highlights" was produced in June 1980. In addition, the Center produced the following DRR directories during the fiscal year:

Biomedical Research Support -- 1st edition
General Clinical Research Centers -- 2nd edition
Animal Resources -- 3rd edition
Biotechnology Resources -- 3rd edition
Minority Biomedical Support -- 3rd edition.

Recognition of the outstanding quality of the Center's products was made with awards to the Center and staff by two nationally known professional organizations: the American Medical Writers Association and the Society for Technical Communication.

In addition, the National Association of Government Communicators awarded First Place in Technical Publications to the DRR Information Officer for "The Seeds of Artificial Intelligence" at its annual awards luncheon. The awards to the RRIC for publications included:

Special Recognition - "The Seeds of Artificial Intelligence: SUMEX-AIM" Publications for Professional Audiences...American Medical Writers Association

Honorable Mention - Research Resources Reporter - Complete Periodicals... Society for Technical Communication

Third Place - General Clinical Research Centers Directory - Industrial Handbooks/Manuals...Society for Technical Communication

Articles in Reporter:

First Place - "Guinea Pig Models Human Diabetes" - Article, Magazines for Professional Audiences...American Medical Writers Association

First Place - "Guinea Pig Models Human Diabetes" - Periodical Articles... Society for Technical Communication

(Note: The above article was entered and received Honorable Mention in Society for Technical Communication International Competition.)

Honorable Mention: "The Problems and Promises of Artificial Intelligence" - Periodical Articles...Society for Technical Communication

Second Place - "Body Chemistry Fuels New Power Cells" - Periodical Articles.. Society for Technical Communication.

As a result of a suggestion by the OSHR Information Officer, the RRIC, through Columbia University, is producing a 20-minute film on the CARTOS neuron-tracing system recently developed at the Biological Computing Facility for Image Processing and Display at Columbia. This film will be used as an instructional tool with the CARTOS loaner system and will also be shown at conventions and conferences of neurological and biotechnical societies. It will also be available at the Center for loan to medical centers and other institutions.

Considerable success was achieved during the year by OSHR in utilizing original Reporter articles for publication in other print media. Among those "recycled" pieces, which were placed by OSHR in slightly modified form, were:

Public Health Reports (Sept.-Oct. 1979) - Lyme Arthritis
NIH Search for Health column (Oct. 1979 - over 500 newspapers) - Diabetes Research in Pima Indians
Brazoport Facts (Dec. 1979) - Children's Milk Allergy
Children Today (Jan.-Feb. 1980) - Reye's Syndrome
News & Features from NIH (Jan. 1980) - Diabesity
JAMA (Feb. 8, 1980) - Diabesity
NIH Record (March 4, 1980) - Human Interferon by Macrophages
Federation Proceedings (April 1980) - Stable Isotope Resource

NIH Record (April 1, 1980) - Alcohol Abuse Causes Impotency
Children Today (May-June 1980) - Down's Syndrome
JAMA (May 2, 1980) - New Treatment for Myoclonus
News & Features from NIH (May 1980) - Alcohol Abuse Causes Impotency
Life & Health (June 1980) - Diabesity
NIH Search for Health column (August 1980) - Biomedical Research Support Program
NIH Search for Health column (Sept. 1980) - Alcohol Abuse Causes Impotency (Both in English and Spanish)

In addition to overseeing the RRIC's activities, the OSHR continued to create more visibility for DRR grant program activities during the year. For example, the OSHR successfully developed and executed a communication program for the University of California, San Diego, GCRC. The plan centered around a series of lectures called the Clinical Research Center "Health Science Tomorrow Lecture Series."

On October 3, 1979, the first lecture--"Fertility, Pregnancy and Birth"--took place in the main auditorium of the University Hospital. The lecture, conducted by GCRC-associated researchers, was attended by a cross-section of lay public residents in the San Diego area, in addition to medical center employees and their families.

On December 5, 1979, the second lecture--"Preventing Cancer, Heart Disease, Gallstones, Ulcers, and Intestinal Problems"--was presented to a near-capacity audience. The third lecture--"Nutrition's Role in Health and Disease"--was conducted to a "full house" on February 6, 1980. The fourth and final lecture--"Is Human Research Necessary?"--took place on May 1, 1980.

OSHR staffers personally participated in and gave overall direction for the lecture series with the cooperation of the San Diego GCRC administrators. A special tubular modular display unit was procured for use at their Annual Hospital Health Fair, and now remains on temporary loan in the lobby of the Medical Center. An extensive promotional plan to inform the public about the value of the GCRC included posters, table tents, and advance notices in the local press. In addition, a series of spot announcement slides with scripts was prepared by OSHR and sent to local TV stations. Radio stations also received copy for public service announcements.

Placements for numerous guest appearances on TV and radio were also made by OSHR for each of the events. Some of these placements include Drs. Alan Hofmann and Paul Jagger, GCRC co-directors, on station KGTV's "Public Pulse," Dr. Hofmann on KFMB-TV's "Sunup San Diego," Dr. Jagger on radio station KFMB's "Here's To Your Health," Dr. J. Edwin Seegmiller on radio station KSON's "Health Watch," Drs. Michael Wiseman and Michael Madigan on radio station KSDO's "Midday," and Dr. Drew Kelts on radio station KPBS-FM's "Afternoon San Diego."

Many stories appeared in San Diego area papers, and several were disseminated nationally over United Press International during the year.

A significant placement was made in the April 1980 issue of the San Diego Physician, the official publication of the San Diego County Medical Society. A 2-page GCRC story was "ghost-written" by OSHR for Dr. Alan F. Hofmann, co-program director of the GCRC, and placed with the magazine. The article describes the history, facilities, and activities of the San Diego GCRC, and has been reprinted for use with the DRR modular exhibit at the Medical Center and for handouts at civic organization or other medical group presentations.

The promotional plan devised by OSHR for San Diego was intended to provide an example to other GCRCs throughout the country. OSHR has recently been contacted by GCRCs at the University of Michigan and the University of California, San Francisco, for assistance in conducting a similar series.

On January 15, 1980, the OSHR assisted in the 10th anniversary celebration of the GCRC at the University of Minnesota Health Sciences Center. In addition to print media coverage, the DRR staffers made radio and TV guest placements for CRC researchers on local stations. Dr. Frederick C. Goetz, GCRC program director, wrote in his letter of February 5th: "Thanks for all your help at our GCRC 10th Anniversary. Your professional assistance was great! The comments and interest we have received continue to be inspiring."

OSHR planned and held a media briefing in Birmingham, Alabama, on February 28, 1980, concerning the development of an effective screening procedure to detect a viral infection common to newborns, believed to be the leading cause of hearing impairment in the U.S.

The briefing, held in the University of Alabama Medical Center building, was attended by science and medical writers, and radio and TV representatives with their technical crews. In addition, during the briefing, a special conference call network was provided by OSHR to medical writers throughout the country. A 1½-minute video tape was prepared and distributed in advance by OSHR.

The resulting press coverage from this briefing was extensive. The story of the new "CMV" screening procedure was flashed over the United Press International, the Associated Press, and other national news syndicate service wires. Victor Cohn, prominent Washington science writer, wrote a feature for the Washington Post which was also distributed over the national Washington Post Service syndicate wire. The story appeared in hundreds of daily and weekly newspapers throughout the country.

An OSHR staffer served on the planning committee for the 8th Annual Minority Biomedical Support Symposium held in Atlanta on April 7-10, 1980. Once again, OSHR managed the press room for the symposium and handled all media activities surrounding the meeting. These included news stories, guest placements on local TV and radio, and national publicity and features which moved on Associated Press and UPI wire services.

Included in OSHR guest broadcast placements were Roma J. Stewart, director of the U.S. Office of Civil Rights; Nobel Laureate Dr. David Baltimore of MIT; Dr. Louis Sullivan, dean of the Morehouse College School of Medicine; and Dr. James Henderson of Tuskegee University.

On April 21-23, 1980, Drs. Jack Myers and Harry Pople of the University of Pittsburgh, demonstrated their computer diagnostic system, INTERNIST, at the American College of Physicians in New Orleans. Working with the communications office of the American College of Physicians, OSHR arranged a special demonstration for the news media covering the ACP meeting. In conjunction with this media demonstration, several other exclusive interviews were arranged for Dr. Myers.

OSHR also developed special flyers to promote the INTERNIST demonstrations to ACP members. "The Seeds of Artificial Intelligence," which describes the INTERNIST system, was made available to the press.

Mr. Mark Christmyer, public information officer of the American College of Physicians, wrote: "I think one of the reasons we were able to get such good coverage from the local media was due to the canvassing you (OSHR) did on the INTERNIST program."

Working with Dr. Daniel Knapp, manager of the CLINSPEC system at the Medical University of South Carolina, the OSHR designed and produced a tabletop exhibit for initial use at the American Federation for Clinical Researchers meeting in Washington, D.C. on May 10-12, 1980. The CLINSPEC exhibit is now on display at the University Hospital in South Carolina and will be booked into various national meetings throughout the year. A special CLINSPEC folder has been produced by OSHR for distribution with the exhibit.

On May 14, 1980, the first Dental GCRC was dedicated at the University of Pennsylvania, School of Dentistry. This event was conceived of and developed by OSHR. A 10-minute film about the dental research activity was produced by OSHR for viewing at the dedication. Clips from this original film were disseminated to TV stations for use on medical and health shows throughout the country. Among the media activities conducted by OSHR at the dedication was the arrangement of an interview for Dr. Irwin Ship with United Press International, placement of Dr. David Friedman on station WFIL-TV show, "For Your Information," and appearance of Dr. Ship on radio station WCAU.

During the past year, continued emphasis was placed on encouragement of grantee institution staff written feature stories on DRR program activities appearing in "house organs" with full DRR identification. Among those reported to OSHR were Center Times, University of Texas; Children's Center Fall Issue, Johns Hopkins University; Khatali News, University of New Mexico; Kaleidoscope, Scripps Clinic and Research Foundation; Health Sciences Record, University of South Carolina; Fairleigh Dickinson University Magazine; and the Southwest Foundation Reporter, San Antonio, Texas.

A feature story on a kidney-transplant patient at the University of Texas GCRC was written and placed by the Office with the Newspaper Enterprise Association. This feature, with a photo of Mr. Owen Dewing in the process of running "at least 45 minutes a day" was sent out over the "major wire" to 750 newspapers on February 2, 1980. Clippings on the story continue to come into the OSHR office from all over the country. "Owen Dewing is still running!"

Further multi-placements on DRR program activities included the story of the new baboon breeding colony at Southwest Foundation; a new dog lungworm discovery at Cornell University; an appeal from Dr. Philip S. Guzelian of the Medical College of Virginia for volunteer patients for a new pesticide poisoning study; and an indepth story on the PROPHET system. These stories appeared in such publications aa ILAR News, LAB Animal, Chemical Week, Laboratory Animal Primate Newsletter, BioScience, News & Features from NIH, the NIH Record, Public Health Reports, Medical Tribune, and others.

The Office assisted in the production of the 1979 Health Career Guidebook, produced by the Division of Associated Health Professions, DHEW. Glossy photos of young scientists in various settings were provided to the editors. The published guidebook, sponsored jointly by the Department of Labor and DHEW, contains 11 photos with full DRR credit lines.

During the year, OSHR handled the production of the following publications:

"Sequences of Immunoglobulin Chains"
"PROPHET Molecules: A User's Guide to the Molecule Facilities
of the PROPHET System"
"PROPHET Statistics: A User's Guide to Statistical Analysis
on PROPHET System"
"Cost Analysis and Rate Setting Manual for Animal Resource Facilities"
"National Survey of Laboratory Animal Facilities and Resources"

In addition, the Office received and processed approximately 20 Freedom of Information requests. Approximately 200 hours of clerical and professional time was spent handling these requests.

The Privacy Act requests, all for copies of summary statements before Council continued to rise. The Office received and processed approximately 111 requests during the fiscal year. This represents about 450 hours of clerical and professional time.

A total of 26,026 publications were distributed through the Office during the year. The Office received 14,835 individual mail requests; 385 individual telephone requests, including Congressional; and 85 individual walk-in requests. Other distribution was made by bulk mail requests, DRR display boards, and at the NIH Visitors Center.

REPORT OF THE DEPUTY DIRECTOR

Dr. James F. O'Donnell

II. Program Reports

Report of the Deputy Director

The major activities of the Deputy Director during Fiscal Year 1980 continued to be the supervision of the Review System and the Program Management System.

Within the Review System, all vacancies on the National Advisory Research Resources Council were filled by the Secretary and the new members were provided with a day of orientation prior to serving at their first meeting. Limitations on our travel budget precluded our ability to have Council members attend selected project site visits as observers to gain an understanding of resources with which they may have little familiarization. Hopefully, we will have greater flexibility in the coming fiscal year to enable us to carry out this valuable activity. Currently, we plan to hold the October 1980 Council meeting in Atlanta, Georgia, where we will have the opportunity to visit several DRR-funded resources at Emory University and Atlanta University.

A new position of Assistant Director for Review was filled this year in response to a long-standing need for full-time supervision of the DRR Review System and to effect a further separation of program from review functions.

Under study this past year have been a series of options related to the review of the Biotechnology Resources Program grant applications. Both the Program staff and the Council have been concerned for the past several years over the lack of uniformity in review of these applications, the majority of which have been reviewed by ad hoc review groups. Beginning this fall, the Division of Research Grants will assign one Executive Secretary this review responsibility. We will be evaluating over several cycles whether this will result in improved scientific merit review.

Significant program activities occurred during this year, especially related to forward planning as a result of the intensive activities related to the preparation of the DRR Five-Year Plan. The Program Directors scheduled planning sessions throughout the year with members of their Initial Review Committees and Council Program Work Groups.

The specific Program-related reports follow:

Animal Resources Program

INTRODUCTION

The overall objective of the Animal Resources Program is to support resource projects that provide, or enable scientists to use effectively, animals in human health related research. Special attention is given to those animal resource activities that are broadly supportive of the missions of the various NIH components. The objectives are accomplished through the Primate Research Centers Program and the Laboratory Animal Sciences Program.

PRIMATE RESEARCH CENTERS PROGRAM

The seven Regional Primate Research Centers (RPRC's) were established with NIH funds during the period of 1961-1965. The Centers and their respective locations are: University of Washington RPRC, Seattle, Washington; Oregon RPRC, Beaverton, Oregon; California RPRC, Davis, California; Delta RPRC, Covington, Louisiana; Yerkes RPRC, Atlanta, Georgia; New England RPRC, Southborough, Massachusetts; and Wisconsin RPRC, Madison, Wisconsin. Each Center is affiliated with a host academic institution. The Centers have unique resources and research environments which are suitable for a broad range of biomedical research. The Animal Resources Program provides core operational support for the Centers through resource grants. Research projects at the Centers are funded largely by NIH categorical Institutes, other Federal agencies and private foundations through grants and contracts which are held by core staff and collaborative/affiliated scientists. Through their use of nonhuman primate models, these scientists have made numerous important contributions to biomedical research. During the past year, investigations have been carried out in various biomedical areas, including reproductive biology, infectious diseases, behavioral sciences, neurosciences, toxicology, nutritional and metabolic diseases and environmental health.

Core support in the amount of $16.131 million provided by this Program in fiscal year 1980 enabled the 138 core staff doctoral-level scientists to conduct research in the Centers. In addition, the resources and services of the Centers were made available to 615 affiliated, collaborative and visiting scientists from various academic institutions. Research training environments were provided for 232 graduate students engaged in thesis related research. The Program provided salary support for 654 doctoral level, technical, and administrative staff personnel.

On a regional basis, the Centers provided a total of over 7,000 biological specimens to 292 scientists at various research institutions throughout the United States. Scientific productivity within the seven Centers has remained strong during the past year, with over 600 journal articles and books published by the core staff and affiliated/collaborative scientists.

Restricted supplies of certain species of feral nonhuman primates (e.g., rhesus monkeys) available from their countries of origin have continued to pose significant and costly problems for the Centers. The domestic breeding programs of the seven Centers produced approximately 1,900 infants and fetuses during the past year, representing nearly 70 percent of their total primate requirements. Small nuclear colonies of a number of less commonly used primate species have been maintained to assure the survival of these species for potential research needs in the future. A total of approximately 12,000 primate animals (45 species and subspecies) were maintained by the Centers during the past year for research and domestic breeding uses.

The major research themes of each Center and selected examples of their research activities during the past year are as follows:

WASHINGTON REGIONAL PRIMATE RESEARCH CENTER, UNIVERSITY OF WASHINGTON AT SEATTLE

The basic research program of the Washington RPRC covers the areas of neurological sciences, cardiovascular function, developmental biology, disease models, endocrinology and metabolism, and craniofacial structure and function. An extensive collaborative program involved over 60 scientists engaged in a variety of investigative areas. An example of research activities at this center is given below.

Link Between Insulin Levels in the Brain and Development of Obesity

It was postulated that body fat, normally maintained within rigid limits, is regulated by some signal which informs brain centers controlling food intake about the present state of body fat. The identity of the signal is unknown, but insulin is a possible candidate. Obese humans have higher levels of insulin in their cerebrospinal fluid than lean humans, and the insulin level for both groups is reduced after a prolonged fast. Scientists at the University of Washington RPRC postulated that the feedback system responding to body fat uses the concentration of insulin in the cerebrospinal fluid as a major signal. To test the hypothesis, they developed a Papio cynocephalus (baboon) model in which feeding was monitored and in which experimental access to blood and cerebrospinal fluid was maintained. The data from these studies showed that the infusion of insulin into the cerebrospinal fluid leads to a reliable and predictable decrease in food intake and reduction in body weight. Insulin appears to be signal which tells the body how fat it is.

The investigators believe that their research may eventually help explain the problem of obesity in humans. Among some obese persons, the brain may not sense the increased insulin levels or other signals in the brain may override the signal from insulin to eat less. However, it is impractical and unwise to administer insulin directly to obese persons. If that were done, it would lower the individual's blood sugar level, creating a desire for food. Thus, the metabolic glucose signal would be, "Eat more," while the insulin signal to the brain would be, "Eat less." The results would be unpredictable. Additional research may be directed to producing a synthetic hormone similar to insulin with an effect only on the brain and not on the metabolic system.

OREGON REGIONAL PRIMATE RESEARCH CENTER, UNIVERSITY OF OREGON HEALTH SCIENCES CENTER

Major areas of research emphasis at the Oregon RPRC have continued to include reproductive biology, perinatal physiology, cardiovascular pathology, cutaneous biology, immunology, nutrition, toxicology, and metabolic diseases and behavior. An example of activities during the past year is as follows:

Polychlorinated Biphenyls, Dibenzo-p-Dioxins, and Dibenzofurans

Polychlorianted biphenyls, dibenzo-p-dioxins and dibenzofurans, the man-made chemicals now found in the general as well as in industrial environments, are highly toxic for mammals. However, species differ greatly with respect to sensitivity and pathologic response. Rhesus monkeys were found to be among the most susceptible animals; following exposure to these agents, they develop changes in the skin that closely resemble chloracne, a human skin disorder considered a hallmark of accidental human poisoning. Lesions that developed on the epidermis, stomach, and thymus of rhesus monkeys after acute or chronic exposure were indistinguishable for the three kinds of compounds. These lesions do not represent cell damage, but alterations in the growth and differentiation of certain specialized epithelial structures. Rhesus monkey fetus is particularly susceptible and small doses of tetrachlorodioxin or biphenyl given early in pregnancy are followed by a high rate of abortion.

The single known biochemical action of these agents is a powerful stimulation of liver oxidative enzyme systems. The exact pattern of this induction is dependent on the molecular location of the chlorine atoms in the offending chemical. The compounds are stable and persistent in the environment. They are a potential threat to human health not only because they are themselves noxious but also because they may synergize with other unrelated toxic chemicals through the mechanism of enzyme induction.

CALIFORNIA REGIONAL PRIMATE RESEARCH CENTER, UNIVERSITY OF CALIFORNIA AT DAVIS

The major research emphasis of the California RPRC relates to environmental health sciences and infectious diseases. Other areas under investigation include perinatal biology, behavioral biology, respiratory physiology and immunology. An example of research activities during the past year is as follows:

Effects of Oral Contraceptives During Early Pregnancy

Investigators in the Perinatal Biology and Reproduction Unit have evaluated the effects of inadvertent consumption of oral contraceptives during early pregnancy in rhesus monkeys. Several retrospective studies in humans have suggested that there is a correlation between sex steroid exposure during early pregnancy and anatomic/behavioral abnormalities in offspring. Norlestrin, an oral contraceptive, was administered to the rhesus monkeys at levels equivalent to two, four and 10 times the recommended human dosage at various periods during early pregnancy. Sixty-three percent of the treated pregnancies produced offspring with no indications of birth defects while 37.7 percent resulted in abortion or stillbirth. The latter level is significantly higher than the spontaneous rate of fetal death in untreated pregnancies. The results of this study indicated that administration of an oral contraceptive to rhesus monkeys during early pregnancy causes an increased level of early fetal death but is not related to a higher incidence of birth defects as previously suggested in humans.

DELTA REGIONAL PRIMATE RESEARCH CENTER, TULANE UNIVERSITY

The Delta RPRC core research programs cover the areas of infectious diseases (a major focus) as well as the areas of immunology, parasitology, biochemistry, neurobiology, and urology. The affiliate/collaborative program includes other areas such as vision research. An example of the research projects underway at the Delta RPRC is given below.

Cornea Attachments for Correction of Visual Defects

This project relates to the development of surgical techniques to correct vision defects by using corneas taken from dead animals. Corneas were surgically removed from donor primate animals, frozen, and shaped on a lathe to certain specifications. While the freezing and thawing procedures did destroy most of the cells, the network of tissue residue that remained was surgically attached to the eye of the recipient primate animal. This nonliving network of tissue was quickly invaded by cells from the cornea of the recipient animal, thus resulting in the desired change in the curvature of the eye. The net effect of this new technique was correction of the vision defect using a living contact lens. These encouraging laboratory results are believed to have great potential for future application to human patients.

YERKES REGIONAL PRIMATE RESEARCH CENTER, EMORY UNIVERSITY

Research at the Yerkes RPRC includes psychobiology of great apes and monkeys, anatomical and physiological aspects of the central nervous system, muscle pathology, reproductive biology, immunology, and language acquisition. An example of their activities during the past year is as follows:

Language Studies

The chimpanzee was used as a behavioral animal model for studies of the requisites to communication skills. The results emerging from this study are related to a companion project with mentally retarded children. Results to date support the conclusion that methods which facilitate learning by chimpanzees are particularly effective in facilitating the learning of severely retarded children. The research with chimpanzees has clearly demonstrated that they are able to use symbols referentially, symbolically, and communicatively, just as humans use words. Two chimpanzees, Sherman and Austin, use their words to request foods and tools of one another, contingent upon tasks to be solved. They have also learned the names for several locations, which will be incorporated into future research. The development of electronic systems and computer systems to facilitate language acquisition by chimpanzees and children is also being pursued.

NEW ENGLAND REGIONAL PRIMATE RESEARCH CENTER, HARVARD UNIVERSITY

The New England Center's core research program covers the areas of infectious diseases, psychobiology, pathobiology, viral oncology, and diseases of primates. The Center's extensive collaborative research program includes numerous other biomedical areas of investigation. An example of research conducted in the core program at the New England RPRC during the past year is as follows:

Behavioral Effects of Drugs

The use of nonhuman primates in research on the behavioral effects of drugs has provided important information that simply could not be obtained from research using human subjects. Pharmacological and environmental determinants of a drug's effects, which would remain uninvestigated in humans, can be easily studied in animals. Especially relevant examples are those studies in which: (1) behavior is controlled by noxious events; (2) chronic drug regimens are employed; (3) the drug being investigated has a high potential for abuse or may produce physical dependence; or (4) behavior has been produced, through appropriate manipulations of environmental histories, that may be considered "abnormal" or maladaptive. Various drugs that have previously been shown to cause neurochemical changes that develop slowly with chronic administration are being studied for their behavioral effects. Since most drugs used clinically to modify behavior are administered chronically, it is important to study their behavioral effects over extended time periods.

Drug dependence is characterized by drug-seeking and drug-taking behaviors that are highly detrimental to the drug-dependent individual and to society. Experimental techniques have been developed so that drug-seeking behavior can be analyzed functionally in the same way as other schedule-controlled operant behavior. Schedule processes are relevant to considerations of drug dependence because behavior developed through such processes can become so powerfully controlled that it preempts other activities and is responsible for continued exposure to the direct effects of drugs. The application of these techniques in current studies should clarify the behavioral and pharmacological conditions that determine the suitability of different drugs as reinforcers. For example, drugs will be compared with respect to the range of different conditions under which they can function as reinforcers. Comparisons of behavior controlled by drug injections and other consequent events will further indicate whether the behavioral processes involved in drug dependence are also operating in various situations not involving drugs. Thus, experimental studies of the behavioral pharmacology of drugs that can function as reinforcers are pertinent to an understanding of drug abuse.

This research has direct human health implications for prevention of drug abuse and treatment of drug dependence. Studies of conditions under which drug-seeking behavior can be enhanced or suppressed by experimental interventions or drug pretreatments will be particularly relevant. Such basic information will be valuable in the design of rational programs to treat drug addiction by behavioral or pharmacological means.

WISCONSIN REGIONAL PRIMATE RESEARCH CENTER, UNIVERSITY OF WISCONSIN AT MADISON

Focused areas of research at the Wisconsin RPRC include endocrinology, behavior, neuroscience, reproduction, and pathology of environmental pollutants. An example of research performed during the past year is as follows:

Studies on Ovarian Function

Puberty is recognized as the developmental stage between sexual immaturity and maturation and has certain striking characteristics which are similar in the human and the rhesus female. After menarchy (the first sign of puberty onset), menstruation occurs very irregularly. In addition, the early pubertal ovary usually fails to accomplish the maturation and release of eggs during the interval between successive menstruations. This period with menstruation, but without ovulation, has been called the period of adolescent sterility and it can last for months or even years. Its regular occurrence as a stage of female development has long fascinated reproductive biologists as a natural mode for fertility control, but an understanding of the mechanisms of this physiological state is poorly developed. Using the rhesus monkey as a model, scientists at the Wisconsin RPRC have uncovered a physiological event that reliably and consistently predicts or signals the time in development when the ovary can release its first egg. Unexpectedly, this essential precondition for ovulation has been shown to be a change in the activity in the brain. The basic phenomenon at puberty can be described as follows:

At a definite time in development, the brain of each individual begins to release large quantities of a chemical that regulates the pituitary ovulating hormone, which is essential for egg development and release. Moreover, the brain releases this chemical substance in a rhythmical manner with much more being released at night than during the day, and this rhythmical pattern is highly efficient in stimulating pituitary ovulating hormone. Special experimental tests have shown that ovulation can occur only after the brain has established its rhythmical release of this important chemical. The brain does not continue its day/night rhythmical release of the chemical throughout adult life. It only does so in rhesus monkeys for a limited period of 10 to 20 months, after which it reverts back to an arhythmical mode of activity. The scientists believe that the brain maintains rhythmical activity as long as necessary to produce maturation of the ovarian system, but the mechanism by which the brain knows when the system has matured is not yet understood.

OTHER PRIMATE RESOURCES

In addition to the Primate Research Centers, the Animal Resources Program supports other primate resource activities. These are as follows:

CARIBBEAN PRIMATE CENTER

This primate resource includes a basic primate colony on the Puerto Rico mainland and semi-free ranging primate colonies on islands off the coast of Puerto Rico. The Center is a valuable resource for research on primate social behavior and tropical disease research. They are currently testing a Dengue type 2/S-1 vaccine and tetanus vaccine in rhesus monkeys. The Center is also an important breeding center for the National Institute of Neurological and Communicative Disorders and Stroke.

PRIMATE SUPPLY

The Animal Resources Program has six contracts and five grants for the domestic breeding of nonhuman primates. In addition, there is a grant for a

Primate Supply Information Clearinghouse. These projects are part of the effort to provide a supply of primates for essential biomedical research in the face of export restrictions and embargoes by the countries of origin. During fiscal year 1980, no wild-caught rhesus monkeys were imported for biomedical research. The supply of other wild-caught Old World as well as New World primates continues to decline due to these increasing export restrictions. The contracts are for the production of animals for general distribution to the NIH extramural investigators. The overall goal of these projects is to provide 1,200 rhesus monkeys, 150 cynomolgus monkeys, and 400 squirrel monkeys per year. As of June 30, we have 1,653 female rhesus, 150 cynomolgus, and 138 squirrel monkeys in production colonies. There were 1,198 rhesus, 91 cynomolgus and 22 squirrel monkeys born this past year. The polio vaccine testing program took the first 250 male rhesus offspring. All females were kept for colony expansion. We supplied 205 rhesus monkeys to NIH grantees from cull, exchange, and recycled animals and have 82 young males to be weaned in the next few months. We have supplied 113 cynomolgus monkeys (adults and young) and 5 squirrel monkeys to investigators. Because of the general difficulties in maintaining optimum squirrel monkey production in captive colonies, grant applications were requested to study the reproductive problems of squirrel monkeys. One grant has been funded and the Government-owned squirrel monkeys maintained on contract will be moved to the grantee institution in the near future. The squirrel monkey contracts will be phased out.

The grant-supported primate breeding projects are for establishing nuclear production colonies and determining proper husbandry techniques for maintaining these colonies. Colonies under development are baboons, two species of marmosets, and owl monkeys.

The Primate Supply Information Clearinghouse is designed to facilitate maximum research utilization of primates already in this country. The Clearinghouse matches requests for primates, primate tissues, and related services with investigators and breeding colonies who have these items available. The Clearinghouse publishes a weekly bulletin and has placed 2,783 primates in the past year. They also published 51 formal requests in their bulletin for cadavers, tissues, and other specimens and handled many more such requests informally by telephone.

LABORATORY ANIMAL SCIENCES PROGRAM

The Laboratory Animal Sciences Program (LASP) assists institutions in developing and improving animal resources for biomedical research and training through the award of research and resource grants and contracts. Program areas include support for research related to improving health care and determining environmental requirements of animals used in research; animal colonies of unusual and and special value for research; studies directed at finding animal models which are needed for research on human diseases; projects to assist institutions to comply with the legal and policy requirements for care of laboratory animals; laboratories for the diagnosis and control of diseases of laboratory animals; and research training of specialists in the field of laboratory animal medicine. The Program awarded funds totaling $7.119 million in fiscal year 1980, which supported 64 discrete animal research and resource projects, eight institutional training programs, and one individual fellowship award.

RESOURCE RELATED RESEARCH

Projects falling into this category generally have one of the following objectives: (1) to investigate the etiology, pathogenesis and control of laboratory animal disease problems or (2) to determine environmental requirements of laboratory animals. For example, currently active projects include the diagnosis and control of mammalian encephalitozoonosis, developing diagnostic/control methods for canine brucellosis, and control of respiratory mycoplasmosis in rodents. The encephalitozoonosis project has resulted in development of a simple, rapid test for detection of serum antibodies in rabbits. Surveys of rabbit populations have reported infection rates of 20-90%, thus demonstrating the potential for complicating research. Ongoing studies are evaluating chemoprophylaxis and continuing to clarify the pathogenesis of the disease and the immunologic impact of infection on the host. In addition to disease related studies, two ongoing projects are focused on population studies of nonhuman primates in countries of origin. These include census studies of rhesus monkeys in northern India and important habitat features relative to West African rain forest primates. The former (India) project was begun in 1959 (supported by ARB since 1973) and has provided data regarding population dynamics, demographic, and reproductive parameters of a natural rhesus population. Within the study population declines of 71% (up to 1977) were noted in an unprotected cohort while a semi-protected cohort increased 186% in the same period. Ongoing studies will provide data on the effects of the current export ban of rhesus monkeys from India, habitat displacement which is occurring with one study group, and the feasibility of intentional transplants and relocation of breeding groups. Such information is necessary as a guide to conservation and management of rhesus monkeys and will be important in evaluating the potential supply of rhesus monkeys for biomedical research.

The number of resource related projects has been relatively level in recent years (9-11 active projects). There is a growing recognition that naturally occurring laboratory animal diseases and environmental factors can have a significant effect on research projects. Clearly, there are many deficiencies in the current state of knowledge relative to many diseases, their recognition, control, etc. In recognition of this need, the support of research projects dealing with important laboratory animal disease problems was selected for emphasis in the recently prepared Five Year Plan. This year three new projects were awarded. The new projects include a study of experimentally induced mucoid enteritis in rabbits (an often fatal disease of undefined etiology) and the pathogenesis of parvovirus infection in canines (a recently recognized, often fatal disease which can pose a threat to breeding colonies and closed colonies of research dogs as well as pet animals).

ANIMAL MODELS AND SPECIAL COLONIES

The major objectives of this program area are: (1) to define, characterize and exploit the relevant biological attributes of selected animals which display potential for use in several areas of biomedical research and (2) to establish, improve or expand special colonies of well characterized animals which are of proven value for biomedical research, but which are not generally available from other sources. Projects aimed at the first objective are of two general types. The first is represented by 3 active resources (Washington State University, the University of Alabama at Birmingham, and Michigan State University) which involve a multidisciplinary effort to identify, characterize, and make available new animal models of human genetic diseases. Input regarding potential models is sought from a variety of sources, including animal clinics, veterinary practitioners, and breeding associations and clubs. The oldest resource of this type is at Washington State University. This group has worked with 30 animal models or potential animal models during the past three years including 7 new ones recognized during this period. Some are now well established and have separate grant support including Ehler-Danlos syndrome of dogs, mink and cats (autosomal dominant disease with defective collagen formation), combined immunodeficiency disorders in horses, and juvenile type diabetes mellitus in dogs. Other models are still in the early stages of development such as mucolipidosis in cats, inherited feline tremors, and inherited canine hyperreninism. The general approach is to establish colonies of affected animals and begin characterization studies, often in collaboration with experts at other institutions who are interested in a specific model. Animals and materials from the various models are made available to interested investigators. Ultimately, some models may be transferred to other groups with the interest and expertise to carry on further studies. Other animal model projects are oriented around selected species which have potential utility as models in more than one categorical area of research. Several marine invertebrate projects, in particular, exemplify this approach. Declining natural populations and problems of maintaining species such as the sea hare, Aplysia californica, sea urchins, Strongytocentrotus purpuratus, and loliginid squids have limited research utilization in the past. Development of mariculture and maintenance techniques could favor laboratory breeding over procurement from the ocean and lead to a continuous source of species wherever they were required. Considerable success has been achieved in maintaining adults of these marine species under laboratory conditions, but much work remains to be done before year-round availability of laboratory reared stocks can be assured.

Special colony projects combine in varying degrees the maintenance and production of special strains or stocks of animals with ongoing research to further development and characterization of the models. Currently supported projects include a hamster resource at the University of Texas, Dallas; a congenic mouse resource at Sloan-Kettering Institute; a rabbit inbred and mutant stock resource at the Jackson Laboratory; and a mouse mutant gene resource also at the Jackson Laboratory. The latter project is typical of this group. The original mouse colony included some 140 mutants with a focus on endocrine, neurological and immunologic problems. The specific aims are to maintain these well defined stocks, including the long term preservation of frozen embryos and to make material available to the scientific community (approximately 1,000 animals per year are distributed to other laboratories either as breeding stock or experimental animals). A charge is made for this service and the funds are returned to the grant. In addition, the resource is interested in adding new mutants to the colony and providing initial characterization and linkage testing. In the case of this resource, the primary source of animals with aberrant phenotypes is the main breeding colony at the Jackson Laboratory which raises over two million mice a year. As an example of this activity last year, a total of 465 phenodeviants were received by the resource and 73 were considered to be of potential scientific interest and kept for further study. Forty-four of these were not recovered in future generations, 10 were discarded and 19 are still being investigated. One example is believed to be the first Y-chromosome mutation found in mammals. This mutation in the mouse mimics one type of abnormal human sexual development; i.e., the occurrence of chromosomally male individuals that develop as females. The study of this Y^h mutation will further our understanding of the role the Y chromosome plays in sexual differentiation. A second new mutation is an autosomal recessive named "twitcher." Abnormal deposits of cellular material characteristic of a lipid storage disease were noted and the enzyme galactosylceramidase was found to be missing. Thus, the twitcher mouse is an authentic model in which to study human Krabbe disease, and hopefully further studies will help find a cure for this now lethal human disease.

Support for projects related to animal model development and the establishment of special animal colonies decreased slightly from the previous year's level; i.e., FY 1979 - $2.201 million (28% of LASP budget) versus FY 1980 - $1.912 million (25% of LASP budget). A total of 24 projects received support, including one new resource grant and five ongoing contracts. The Five Year Plan provides for a continuation of animal model and special colony activities at approximately the same or a slightly reduced level. Emphasis will be given to model development and characterization as opposed to preservation and maintenance in considering new projects.

INSTITUTIONAL ANIMAL RESOURCE IMPROVEMENTS

Institutional animal resource improvement projects are awarded to help institutions upgrade their animal facilities and develop centralized programs of animal care in support of their biomedical research programs. A major objective is to enable institutions to comply with the Animal Welfare Act and DHHS policies on the care and treatment of animals. Requests of this type usually include animal cages to meet current regulations, general sanitation equipment such as cage washers, renovation of animal facilities, and addition of trained professional and technical personnel. The projects are supported for one to three years, after which time the applicant institution is expected to take over complete financial responsibility for its basic animal resource.

Institutional improvement projects have been supported since the inception of the Laboratory Animal Sciences Program. Requests of this type peaked in FY 1973 following implementation of the Animal Welfare Act of 1970 (P.L. 91-579) and the DHHS policy on animal welfare. Over the past eight years, 93 institutions have received improvement grants with awards totaling approximately $12.2 million. The following figures represent the trend during this period:

	FY 74	FY 76	FY 78	FY 80
Reviewed	19	19	21	12
Approved	12	9	13	8
New Awards	36	6	3	4
Total Active Projects	46	21	11	6
$ Awarded (in $1,000's)	3229	1289	793	783
Percentage of Budget	51%	23%	10%	10%

The above chart indicates a relative steady rate of new proposals in recent years. The largest number of program inquiries still touch on this area. The ability to fund new projects of other types and to combat inflationary costs has come largely at the expense of this program area (note steady decrease in number of active projects and $ awarded). It was possible to fund four new proposals this year, and it appears that at least this level of funding should be maintained for the next several years.

Data from the recently completed National Survey of Laboratory Animal Facilities and Resources (published March 1980; FY 1978 data) revealed the following relative to facilities and equipment:

- Approximately 16 percent of all nonprofit biomedical research organizations reported a need for replacement of some animal facility space now in use, 38 percent reported a need for remodeling to protect the integrity of space now in use, and 43 percent reported a current need for additional space.

- Approximately $350 million is required to meet current needs of nonprofit biomedical research organizations for space replacement, remodeling, and additions. Another $407 million (using FY 1978 estimated construction costs) will be required to meet space needs projected for FY 1988.

- Nonprofit biomedical research organizations reported a current need of $43 million for equipment renovation, replacement or additions.

The survey indicates in particular a need for biohazard containment space and equipment, which reflects changes in research activities and increased recognition of the need to contain hazardous agents. In order to meet needs of the scale indicated by the survey, legislative authority (new construction and major renovation) and substantial funding over a period of years would be required. This will require careful assessment from the perspective of the NIH at large and may well not be feasible in the immediate future.

RESOURCE LABORATORIES

The objectives of these laboratories are to provide for improved animal health programs through investigation of naturally occurring disease and related laboratory animal problems, to support studies resulting in new information on diseases of laboratory animals and their etiology, to aid in the elucidation of new laboratory animal models of human disease, and to develop resources including tissues, slides, photographs, etc., for research and training. Resource laboratories have been a major program activity for over 10 years. There has been a continuing turnover in the institutions receiving such awards (support has been terminated for 13 laboratories). The total number has remained relatively constant (13-16) in recent years and approximately 28% of the budget is awarded in this area. Since resources and trained personnel are limited, laboratories have been confined to those settings with at least several million dollars of NIH-supported research involving the use of laboratory animals. Most resource laboratories are institutional in nature; however, in several instances it has been feasible to serve more than one institution in a metropolitan or regional area. There are sixteen programs which are currently being supported. One new laboratory was funded during FY 1980.

Laboratory activities encompass a broad spectrum ranging from surveillance and monitoring to conduct of research on important laboratory animal disease problems. The laboratories have been productive in terms of new information and techniques. It is apparent that a multidisciplinary approach to disease problems is necessary in order to identify and isolate etiologic agents and then take appropriate steps to eliminate or control the problem. The interaction of clinicians, virologists, and pathologists was well illustrated by one resource when presented with the problem of shortened survival time in mice inoculated with Sarcoma 180. Focal liver necrosis was noted at necropsy, along with lesions due to the transplanted tumor. Microbiological tests were negative. Subsequent study of pooled tumor cells inoculated into suckling and adult mice and tissues culture plus fluorescent antibody tests confirmed the presence of LCM virus. An aggressive quarantine was established, and mice carrying known or suspected infected tumor lines were killed. In a follow-up epidemiologic investigation, it became apparent that other laboratories were having unexplained variances from anticipated results when using certain tumor cell lines, and LCM virus was ultimately isolated from five laboratories and 15 tumor lines. Forty-five persons were serologically tested and one was positive. The timely recognition and control of this problem eliminated the risk of human exposure as well as the publication of data from animals compromised by a latent viral infection. Another resource laboratory became heavily involved in the recent outbreak of ectromelia that appears to have originated in mice at the Clinical Center on the NIH campus. The resource was contacted when a serious disease outbreak occurred among 30,000 mice at the University of Utah Medical Center in Salt Lake City. The clinical signs consisted of swelling of the face and head, conjunctivitis, and acute death--often within 3-6 hours. Some survivors had severe skin lesions including loss of feet and tails. The disease was confirmed as being ectromelia by serologic tests, characteristic lesions, electron microscopy, and clinical signs. The resource was involved in reviewing decontamination procedures, vaccination and formulating recommendations for general management and renovation of the facilities. Approximately 10,000 mice were killed and an additional 20,000 were vaccinated. The disease achieved a substantial foothold at this institution, but two-thirds to three-fourths of the animals were saved by the prompt diagnosis and control measures. In this outbreak, the loss in animals alone was estimated at $600,000; but lost time on the part of investigators, decontamination, etc., would magnify this figure several times. Thus, the potential impact is apparent if the disease had not been localized and controlled before spread to other animal facilities in this country or abroad.

Recognition of potential animal models is an important aspect of working up problems presented to the laboratory. One laboratory recently reported the occurrence of diabetes mellitus in degus (Octodon degu). Inclusion bodies were demonstrated in islet, acinar, and ductual cells of the pancreas from some of the degus with clinical signs of diabetes. Electron microscopy revealed many spherical DNA virus-like particles similar in size and shape to cytomegalovirus particles in man and other animals. The presence of insulitis, characteristic inclusions of cytomegalovirus in the pancreas and clinical evidence of islet dysfunction suggested viral infection as the cause of diabetes in these animals. Studies are underway to isolate the virus in cell culture and further define its relationship to diabetes. This model offers considerable promise in helping understand the possible relationship between cytomegalovirus and islet cell function in man since there are a number of reports of generalized cytomegalovirus infection in infants and signs of infection in several organs, including the pancreas. Solution of individual clinical problems can also be important when dealing with valuable laboratory animals such as nonhuman primates. Intermittent diarrhea and chronic weight loss over a two year period was noted in a female adult stumptail macaque when fed a commercial laboratory maintenance diet. Extensive laboratory workup plus a favorable clinical response to dietary substitution resulted in a diagnosis of lactose intolerance. As added findings, it was noted that Ketamine HCl used to restrain unconditioned macaques during lactose intolerance tests adversely affected the establishment of baseline plasma glucose tolerance curves. Thus, repetition of the tests after chair-conditioning the animals to produce clear baseline control data against which the lactose intolerant animal could be compared was necessary. This is the first report of clinical disease associated with lactose intolerance in this species.

REFERENCE CENTERS AND INFORMATION PROJECTS

The Program supports several reference center and information projects. These include the Simian Virus Reference Laboratory at the Southwest Foundation for Research and Education, San Antonio, Texas (diagnostic virology, serology and consultation service); a Blood Group Reference Laboratory at New York University School of Medicine (nonhuman primate blood typing); an Animal Model Reference Center at Texas A&M University, College Station (sperm bank for animal models); and publication of the Laboratory Primate Newsletter. The range of activities encompassed by projects of this type is reflected by the following examples:

1. The Registry of Comparative Pathology, located at the Armed Forces Institute of Pathology. The Registry has continued to augment its collection of specimens from primates and other laboratory animals, domestic and wild animals, fish and birds (over 1,600 accessions during the last reporting period). Material has been made available to others and utilized for the preparation of exhibits, lantern and microscopic slide sets and as the basis for a number of publications. In addition to responding to numerous outside requests for consultation, the Registry publishes a quarterly Comparative Pathology Bulletin to promote communication and information dissemination to the biomedical community (over 3,100 names on present mailing list). Since 1972 it has been responsible for preparation of one or two descriptions of an animal model of human disease for publication each month in the American Jounal of Pathology. A handbook entitled "Animal Models of Human Disease" has been prepared for sale. Eight fascicles covering 180 models plus a cumulative index have been published so far. An annual short course (3 days) in comparative pathology was offered for the seventh time in May 1980. Also, this year a workshop entitled "Needs for New Animal Models of Human Disease"

was held in April at NIH. The proceedings of this workshop will be published as a supplement to the American Journal of Pathology.

2. An Immunohematological Reference Center located at Michigan State University. This reference center was established to produce, standardize, and unify the resources available that recognize red blood cell groups, histocompatibility antigens, and other immunogenetic markers in the dog. The canine erythrocyte blood group system has been operational for a number of years. Efforts in the past year focused on reagent production for histocompatibility antigens. Collaboration with other investigators by providing reagents and typing services has increased and has been a major commitment of the Center. During the last reporting period, a total of 264 animals were typed for erythrocyte antigens, 279 were characterized for histocompatibility antigens, and 382 ml. of various typing sera were provided to qualified investigators.

TRAINING

Training in laboratory animal medicine is intended to prepare individual to provide professional care of the many species of laboratory animals, to manage central animal resources, and to give special assistance to investigators through knowledge of laboratory animal biology and understanding of research methods. In addition, the trainees are prepared to participate in the teaching of graduate students and young investigators and to pursue their own research interests either as independent investigators or as a member of a research team.

There are eight currently active training programs with a total of 29 funded trainee positions. In addition to the institutional programs, one individual postdoctoral fellowship was active at the end of the fiscal year. Since the average training period is two and one-half years, there are usually 8-10 graduates per year. Currently available figures indicate that 154 trainees and fellows have completed training since the inception of training grants and fellowships in laboratory animal science and medicine. Fifty (50) of these are employed by medical schools and 60 by other academic, research or governmental organizations. The majority (89) are serving as directors or staff members of a vivarium; 52 are engaged in research or obtaining additional training; and 13 are in public health, private practice or are retired. Retention in the field of laboratory animal medicine has been excellent, emphasizing the career orientation provided by the training and the continuing need and opportunities available for such individuals.

For the past five years, the active training programs and diagnostic resources have been encouraged to employ veterinary students during their summer break. Seven programs and 13 students participated this past year. Critiques of the students involved were submitted to the Branch and, in turn, distributed to all the program directors. It appears that this work experience is resulting in greater knowledge and interest in the field of laboratory animal medicine by veterinary students. Several former summer students entered formal postdoctoral programs this year and development of a "pool" of such individuals for future postdoctoral training should result in long-term benefits to the field.

Table I

Primate Research Centers Program Applications - FY 1980

Type	Number Rec'd	Amount Requested 1/	Number Appr	Amount Approved 1/	Number Funded	Amount Funded 2/
New.........	-	--	-	--	-	--
Renewal.....	1	2,801,125	1	2,614,256	1	14,001,517
Supplemental	-	--	-	--	-	--
Continuation	6	15,711,124	6	14,828,800	6	2,129,603
TOTALS	7	18,512,249	7	17,443,056	7	16,131,120

Table II

Laboratory Animal Science Program Applications - FY 1980

Type	Number Rec'd	Amount Requested 1/	Number Appr	Amount Approved 1/	Number Funded	Amount Funded 2/
New.........	40	4,588,962	34	3,118,881	11	1,244,295
Renewal.....	18	2,602,340	17	1,915,201	9	1,416,102
Supplemental	11	250,223	11	188,592	10	149,046
Continuation	36	3,211,810	36	2,571,627	34	3,666,367
TOTALS	105	10,653,335	98	7,794,301	64	6,475,810

Table III

Laboratory Animal Science Programs - FY 1980

Program	Number Rec'd	Amount Requested 1/	Number Appr	Amount Approved 1/	Number Funded	Amount Funded 2/
Resource Research	24	1,495,391	24	1,223,077	11	664,881
Primate Resource.	10	1,142,043	9	936,058	4	429,042
Special Colonies and Models.....	26	2,015,526	25	1,655,532	19	1,705,529
Basic Improvement	14	2,300,185	10	1,169,143	6	783,004
Diagnostic Labs..	21	2,952,317	21	2,210,392	16	2,203,829
Reference........	5	634,666	5	492,167	4	550,047
Info. & Other....	4	88,207	3	82,932	3	100,797
Research Career..	1	25,000	1	25,000	1	38,681
TOTALS	105	10,653,335	98	7,794,301	64	6,475,810

1/ Direct Costs Only
2/ Includes Indirect Costs

Table IV

Contract Program - FY 1980

Program	Number Supported	Amount Funded
Special Colonies and Models	5	206,021
Primate Resources..........	1	150,000
Primate Supply.............	5	804,149
Program Support............	4	145,900
TOTALS	15	1,306,070

Table V

National Research Service Award Program - Institutional - FY 1980

Type	Number Rec'd	Amount Requested 1/	Number Appr	Amount Approved 1/	Number Funded	Amount Funded 2/
New.........	-	--	-	--	-	--
Renewal.....	2	233,840	2	282,560	2	113,684
Supplemental	-	--	-	--	-	--
Continuation	6	460,017	6	460,017	6	507,909
TOTALS	8	693,857	8	742,577	8	621,593

1/ Direct Costs Only 2/ Includes Indirect Costs

Table VI

National Research Service Award Program - Individual - FY 1980

Type	Number Received	Number Approved	Number Funded	Amount Funded
New.........	-	-	-	--
Renewal.....	-	-	-	--
Supplemental	-	-	-	--
Continuation	1	1	1	21,382
TOTALS	1	1	1	21,382

Table VII

Short Term Training Program Applications - FY 1980

Type	Number Rec'd	Amount Requested 1/	Number Appr	Amount Approved 1/	Number Funded	Amount Funded 2/
New.........	7	198,320	7	119,930	1	13,025
Renewal.....	-	--	-	--	-	--
Supplemental	-	--	-	--	-	--
Continuation	-	--	-	--	-	--
TOTALS	7	198,320	7	119,930	1	13,025

1/ Direct Costs Only 2/ Includes Indirect Costs

Background and Summary of Past Accomplishments

The Biotechnology Resources Program (BRP) was initiated in 1962 in response to a Congressional interest that NIH establish an activity focused on specialized equipment needed for biomedical research. Since that time, the BRP (formerly called Special Research Resources) has changed and expanded its scope. While the program in the early years, mainly supported large general purpose computer centers in medical schools, it later moved into an extremely broad and innovative array of biomedically relevant technologies. In addition, the program now places greater emphasis on broad-based sharing of resources. Major thrusts of the program today are applications of biomedical engineering, computer science and knowledge systems to biomedical and clinical research programs, and development of specialized instrumentation for the study of biological structure and function.

Technical capabilities provided by the BRP continue to be essential for progress in many areas of scientific investigation. Without advanced technological resources, biomedical research scientists would be unable to make important morphological and chemical measurements or to handle the vast amount of data required to reach valid scientific conclusions.

Over the years, physical and mathematical theories have been developed and subsequently used by engineers in order to responsively provide important research instrumentation necessary for solving problems in biomedical research. That interface between scientists and engineers, so essential for the scientific advancement of biomedical knowledge, is not always obvious nor easily established. Through its operation at this interface, the BRP has been able to develop and make available advanced, highly sophisticated research tools for biomedical science.

BRP has developed and made available to scientists a wide range of computer systems for study of biomedical problems. Among the more recent are computer systems for applying artificial intelligence methods to biomedical problems, computer graphics systems for study of three-dimensional structure of proteins, nucleic acids, interactions of proteins and drugs, and structure of nerve cells and fibers. The development of the first high field 600 MHz nuclear magnetic resonance spectrometer for biomedical research was supported by BRP in collaboration with NSF. BRP introduced the first million volt electron microscopes dedicated to biological research in this country and in the world and supports high resolution scanning transmission electron microscopes used in resolving single atoms in cells and tissues.

FY 1980 Accomplishments

Administrative -- New Resources

BRP funded four new resources this fiscal year. Two resources offer new specialized equipment and technology not available elsewhere on a shared basis. A Synchrotron Radiation Biotechnology Resource was established at Stanford University for use of synchrotron radiation in biomedical research studies involving X-ray diffraction, X-ray spectroscopy and fluorescence measurements. Initial research will be on characterization of metal containing proteins using extended X-ray absorption fine structure techniques and the determination of protein crystal structures using anonolous X-ray scattering information from single crystals. The former method takes advantage of the high intensity of synchrotron X-radiation and the latter studies require tunable wavelength capability for effective use. Access to a laser microbeam instrument is now possible for scientists, with the opening of the "Laser Microbeam Biotechnology Resource" at the University of California, Irvine. It is able to perform subcellular, cellular, and tissue level microsurgery on cells in vitro or in the organism.

A Scanning Transmission Electron Microscopy Resource was established at Johns Hopkins University. The research focus will be on the localization of heavy atom stains on proteins, nucleic acids and cells. Mass spectrometry applications in pharmacology and clinical medicine will be emphasized in the "Clinical Mass Spectrometry Resource" established at the University of Colorado Medical School, Denver.

Workshops, Conferences, and Exhibits

Six conferences or workshops were held in Fiscal Year 1980. The Stanford Magnetic Resonance Resource held its fifth annual conference on molecular structural methods in biological research on November 19-20, 1979, at Stanford University. A workshop on simulation and simulation resource was held on December 16-19, 1979, at the University of Washington Continuing Education Center at Lake Wilderness. A meeting to discuss problems and opportunities in the area of scanning transmission electron microscopy was held on December 10, 1979, in Bethesda, Maryland. The capabilities of 600 MHz Nuclear Magnetic Resonance Spectrometers were discussed in a symposium held in December 1979 in Pittsburgh. On June 4-6, 1980, a Conference on Implantable Transducers and Systems: Closed-Loop Physiological Control was held at the Biomedical Electronics Resource, at Case Western Reserve University. The 6th Annual Artificial Intelligence in Medicine Workshop was held at Stanford University August 13-16, 1980, and the Annual PROPHET Users' Colloquium was held on May 15-17, 1980, at Airlie House, Warrenton, Virginia.

BRP showed an exhibit featuring the BRP Resource Directory and Program Guidelines at Federation of Associated Societies in Experimental Biology Meeting in Anaheim, California, April 13-18, 1980, and at the American Society of Biological Chemists and Biophysical Society in New Orleans, Louisiana, June 1-5, 1980.

Research Accomplishments -- Biomedical Computing

A striking development at the Computer Graphics Resource at the University of California, San Francisco, is the first demonstration of real time interactive color surface graphics. It is now possible to display and interact with 3-dimensional (3-D) computer representations which combine both skeletal structures (labeled if necessary) and surfaces of molecular models. This combination is impossible with present real space models.

The surfaces correspond to the "solvent accessible" regions of the molecule defined by interacting with an idealized water molecule. The addition of the skeleton gives a sense of stereochemical scale and allows inter-atomic distances to be clearly demonstrated. Full use is made of the power of the Evans and Sutherland Picture System II color display. The molecules can be easily distinguished by color (and/or the atoms can be color codes -- both skeletal and surface); depth cueing and real time rotation together with optional time-separated stereo, allow full 3-dimensionality. The 3-D clipping planes allow selection of appropriate section for viewing and even permit views from the inside, as well as the outside. All of this can be manipulated in real time and is being actively developed for use in drug design. A feature article on this work appeared in Chemical Engineering News, July 21, 1980.

During the past year, Drs. Earl Zimmerman, David Margulies, and William F. Marovitz of the Department of Neurology, Columbia Presbyterian Medical Center and Anatomy Department of Mt. Sinai Medical Center, have initiated a collaborative study with the staff of the Computer Graphics Resource at Columbia University on peptides and other chemical compounds which modulate neuroactivity in the central nervous system of mammals. A relational data base incorporating three dimensional (3-D) structural data and significant functions of these modulators have been assembled by these investigators. This data base called NEURONET, which uses the Resource's capability of relating 3-D structure to other data, permits a new level of clarity in the integration, storage, retrieval, and communication of basic neuroscientific findings from different laboratories.

An extensive rat brain atlas has been entered into the resource computer system at Columbia so that the whole brain or any portion of it can be studied in 3-D. The distribution of multiple peptides in a single region of brain has been studied. In particular, the relationship between the vasopressin cells of rat paraventricular nucleus and cells containing oxytocin, enkephalin, angiotensin II, neuroteinsin, and cholecystokinin, was examined. This work is being continued to create a detailed atlas of peptide distribution fields. This is of particular interest because the distribution of bioactive substances does not always adhere to the contours of nuclei or brain regions. It may well be that structure-function correlations are best sought to the contours of neuromodulator distribution fields rather than to the contours of brain nuclei. A logical extension of the work with the rat brain atlas is the creation of a three-dimensional human brain atlas by tracing serial sections of human brain (from a standard stereotactic atlas) into the computer system. With the assistance of Drs. Hawrylyshyn and Tasker (Toronto General Hospital), the Columbia resource has now created the first portions of a computer-based human atlas. It is anticipated that such an atlas will permit the development of an interface to CAT (Computerized Axial Tomography) scan output and permit a new level of information in human structure-function studies.

The project in "Pulmonary Function Test Interpretation and Ventilator Management" (PUFF/VM) at the Stanford University Medical Experimental Computer Resource (SUMEX) interprets standard laboratory measures of pulmonary function, including measured flows, lung volumes, pulmonary diffusion capacity, and pulmonary mechanics. It prepares a report for the patient record, explaining the clinical significance of measured test results and tentatively diagnosing the presence and severity of pulmonary disease for review by a physician. The ventilator management program, VM, still in early development stages, is being designed to interpret the clinical significance of physiological data from patients in the intensive care unit. The interpretation will be used to assist in managing patients receiving ventilatory assistance by providing a summary of a patient's physiological status, recognizing unusual events in the patient-machine system, and providing suggestions for appropriate therapeutic action. The PUFF program has been transferred to a computer at Pacific Medical Center, where it has been in routine daily use for over one year. Currently it uses about 150 pulmonary physiology rules to interpret results. Over 80% of the reports are accepted by the reviewing physician without change, signed, and entered into the patient record. Most of the remaining reports require the addition of a comment about the relation between current and previous test results -- a manual step that is necessary because the PUFF system does not yet have historical test data available on the computer.

Over the past two years, the Washington University Resource for Biomedical Computing has collaborated with the American Heart Association (AHA) under contract with the National Heart, Lung, and Blood Institute, to develop a carefully documented database for the evaluation of dysrhythmias detectors. Despite the seriousness of the clinical problems addressed by dysrhythmia detectors, there has existed no agreed-upon method for evaluating the adequacy of their performance. The final database, to be released upon completion of documentation, contains 160 three-hour recordings covering eight dysrhythmia classes. A panel of nationally recognized experts from four universities has selected examples from among 400 candidate recordings submitted by 17 institutions from six countries. The nature of every heartbeat in the last 30 minutes of each of the selected recordings is then designated by another panel of distinguished electrocardiographers from three universities. Logistic and technical support for soliciting, screening, processing, analyzing, reviewing, and documenting the content of each 24-hour candidate recording and the final choices therefrom, is provided by the Washington University Resource. The technical capability for doing so is the direct result of sustained BRP funding of fundamental research to develop and support a high-performance computer-based ECG analysis system. Benefits of this effort will accrue to patients, medical practitioners, purchasers of monitoring or analysis systems or services, system developers, and agencies concerned with technology assessment and regulation. The tools are now in hand for performing the sorely needed evaluations which will foster a mechanism to assure the consumers of the integrity of the information upon which life-saving decisions are made.

A study of immunoglobulin protein and nucleic acid sequences is being conducted by by Dr. E.A. Kabat of Columbia University in New York and the NIH, in collaboration with Dr. T.T. Wu, at Northwestern University in Evanston, Illinois using the PROPHET National Computer Resource. This cooperative study has resulted in extensive publication in scientific literature as well as an automatically computer typeset compendium of all known Sequences of Immunoglobulin Chains. This compilation is essential to understanding how antibodies are generated and how genetic information for antibody specificity is stored in the DNA and transmitted from generation to generation.

Biomedical Engineering

Drs. Barry Dworkin and Neal M. Miller, behavioral scientists at the Rockefeller University Computer Research Resource, have developed a method to treat idiopathic scoliosis (which usually ends in lateral curvature of the spine) by employing the techniques of biofeedback. Scoliosis is usually treated by surgery or by having the patient wear a cumbersome and move restricting Milwaukee brace. The patients in this project wear a light-weight, small, battery-powered device which detects undesirable posture shifts by means of two flexible bands placed about the torso. A miniaturized electronic circuit uses digital logic to respond to these postural shifts. After a prespecified time delay, an audio oscillator is turned on at low volume so that a faint tone is heard by the patient. If the improper posture is corrected, the oscillator is turned off. However, failure to correct the postural shift within a certain time interval will result in a much louder tone being produced. At present, 16 young women are participating in a study and preliminary data is encouraging with respect to slowing down the increase in lateral curvature or arresting any further increase.

A miniature thermometer array developed in the Resource for Silicon Biomedical Transducers at Stanford University provides an essential tool to cancer researchers who are studying the reversal of tumor growth by localized heating of the tumor through application of electromagnetic waves. The array, injected into living tissue within a hypodermic needle, may be left in place for short-term or long-term measurements. It monitors temperature at several points so that tumor cells are heated to a high enough temperature and healthy tissues are not over heated. The usefulness of the thermometer array has already been demonstrated in short-term animal experiments.

An inflatable vest for measuring cardiac signals has been developed by the Biomedical Electronics Resource at Case Western University. Three sizes of vests and associated electronic circuits, that obtain surface potential signals at 180 points across the dorsal surface, have been designed, fabricated, and evaluated. The system operated by a nurse is being used routinely at Rainbow Babies and Children's Hospital to make recordings on magnetic tapes. The overall goal of the project is to correlate potentials on body surfaces with cardiac physiology and pathology in pediatric patients undergoing catherization to obtain a data base on normal and abnormal patients. It is anticipated that by using the different methods of displaying potential maps, the superior diagnostic capability of this technique over conventional cardiography can be demonstrated. The technique called body surface potential mapping for cardiac diagnosis may have great significance in determining the nature of the disease and treatment for cardiac patients, particularly children.

Biological Structure and Function

The 600 MHz NMR spectrometer at Carnegie-Mellon University was completed and evaluated during this fiscal year. The capabilities of the spectrometer were described at a symposium held at the Biotechnology Resource in Pittsburgh in December, and the instrument is now being used by a number of scientists throughout the country.

Reye's Syndrome is a potentially deadly condition which strikes children between the ages of two and 20, usually after an influenza B, German measles, or chicken pox infection. A researcher from Tufts University developed an in vitro assay of mitochondrial oxidation which correlated well with clinical stages of the disease, and has been collaborating with the MIT Mass Spectrometry Facility to identify the compound involved. After several years of work, the unknown compound was isolated and found to be uric acid. This result makes it possible to use a routine clinical test (uric acid level) to assist the diagnosis and follow the course of the disease.

Recently the Stable Isotope Resource at the Los Alamos Scientific Laboratory completed a 700-foot long distillation plant for the enrichment of the stable isotope carbon-13 from its natural abundance level of 1.1 atom % to an isotopic purity greater than 99 atom % by the low temperature distillation of carbon monoxide. With the addition of this latest plant, the Resource can now produce routinely all the stable isotopes of the key elements in living systems. The isotopes are incorporated into natural products and drugs for research uses, including metabolic studies for the early detection of disease, pharmacokinetic and bioavailability studies of drugs and structural investigations of enzymes.

The Brookhaven Scanning Transmission Electron Microscope Resource has developed the capability for high accuracy mass measurement on small particles visible to the electron microscope. The technique takes advantage of the linear relationship between the electron scattering power of the specimen and its molecular weight. The Brookhaven STEM uses a cold stage to minimize mass loss during measurement, a freeze drying and vacuum transfer system to avoid drying artifacts, and a data acquisition and analysis system optimized for quantitative mass measurements. Applications have included determination of the number of subunits in the active complex of a biotin enzyme complex and a reconstituted chromosomal subunit.

Introduction

During the past year, the program has reviewed and analyzed program progress during the past ten years. Particular attention has been paid to the analysis of the General Clinical Research Centers (GCRC) Program with respect to the overall DRR mission and its relationship to the needs of the NIH. An analysis of the overall scientific merit of studies utilizing CRCs has been made. The distribution of GCRC dollars to U.S. institutions has been shown to correlate closely with the distribution of NIH funds for grants to physicians involving research with human subjects. Portions of these analyses have been presented to the NIH Research Resources Coordinating Committee and DRRs advisory committees where they have been favorably received. A paper titled Clinical Research Perspectives from the General Clinical Research Centers Program was presented to the Institute of Medicine Conference on Clinical Investigations in the 1980s: Needs and Opportunities.

During the 1970s, application of new program policies together with intensified scientific peer review has resulted in a program substantially different and improved from its counterpart of ten years ago. In 1969, there were 92 centers with 1016 beds, with a mean priority score of 251. Since 1969, 32 of these centers, with 269 beds, at a mean priority of 310, have been terminated. The remaining 60 centers, funded in 1969 with 757 beds, have been reduced to 523 beds. The space for the 234 beds eliminated from these 60 centers has been converted to space for outpatients, revenue-producing C patients, and storage. The outpatient space, including treatment rooms, waiting rooms, examining rooms, and offices, has been staffed by existing center personnel. The 20,000 C patient days per year generate about two million dollars in revenue, helping to offset the personnel cost of operating the centers. Plans call for use of some of the remaining storage space for data management resources (CLINFO) and support staff for the centers. During the ten year period since 1969, 12 new centers, with 82 beds, have been added to the program, with an average priority score of 207. Five of the 32 centers which were terminated have reappplied and competed successfully for 27 beds.

In summary, then, in 1969 the program supported 92 centers with 1016 beds, with an average priority score of 251, while in 1980 it supports 75 centers with approximately 600 research beds and 76,000 outpatient visits, with an average priority score of 213. The average length of patient stay decreased from 10.4 days in 1969 to 5.7 days in 1979.

Program Content and Quality

The program supports 80 percent of the research inpatient care for the extramural program of the NIH. More than 3000 projects are conducted on the centers each year by an even greater number of investigators, most of whom receive support from research grants, training grants, program project grants, NIH contracts, or career development awards. Except for the absence of the larger clinical trials, the program content is reflective of the NIH clinical research program as a whole. More specifically, in 1978 investigators using the centers were supported by 2100 NIH grants and contracts totaling $270,000,000 (Table I). An additional estimated $30 million was received by investigators from research foundations and societies, industry, and other sources.

Another way of looking at program content is by broad disciplinary categories (trans-NIH activities). In 1977, the centers reported 433 projects, costing $10,150,000, in nutrition; 578 projects, costing $7,242,000, in genetics; 330 projects, costing $5,962,000, in diabetes; and 91 projects, costing $1,540,000, in arthritis. Of course, some of these categories (e.g., nutrition and diabetes) are not mutually exclusive, but they do give some idea of program support in a few research areas of great public interest.

Measures of program quality are somewhat more difficult to make, since one is always confronted with the question, "Quality compared to what?" In terms of publications, the program has had a more than 50 percent increase in output since 1970 (Table II). Moreover, there has been a steady increase in publications resulting from outpatient studies. Thus, the program seems to be far more productive than it was ten years ago despite the substantial decrease in the number and size of centers supported.

A recently completed priority score study provides some information on the level of quality. At site visits, investigators using the centers are ranked on a scale, like that used by the NIH study sections, by site visit teams which are composed of national experts in the fields being reviewed and which are comparable to the NIH study sections.

In this study, the priority scores awarded to individual investigators at site visits in 1976 were compared with their utilization of patient days and outpatient resources in 1977. In 14 consecutively reviewed centers, 82 percent of the patient days were utilized by investigators whose work had been assigned priority scores at the DRR site visit; 18 percent of the patient days utilization was by new investigators. Of the usage for investigators assigned a priority score by DRR reviewers, about 61 percent was by those who received a priority score between 100 and 200 at the site visit, and 31 percent was by investigators who had

TABLE I

ESTIMATED PHS SUPPORT FOR INVESTIGATORS USING GCRCs BY INSTITUTE FOR FY 1978

Institute	Number of NIH Grants and Contracts Awarded to Investigators Using GCRCs	Awarded Dollars (Millions)
National Institute of Arthritis, Metabolism, and Digestive Diseases	650	$ 58.9
National Heart, Lung and Blood Institute	443	89.8
National Cancer Institute	274	37.4
National Institute of Child Health and Human Development	194	19.3
National Institute of Allergy and Infectious Diseases	154	12.8
Other Public Health Sources	125	9.6
National Institute of General Medical Sciences	104	17.0
National Institute of Neurological and Communicative Disorders and Stroke	96	16.2
Division of Research Resources1/	30	2.9
National Eye Institute	24	1.9
National Institute of Aging	13	1.1
National Institute of Environmental Health Sciences	12	1.0
National Institute of Dental Research	9	2.1
Total	2128	$270.0

1/ Exclusive of GCRC Awards

TABLE II

CENTER PUBLICATIONS

Year	Publications	(Publications Involving Outpatients)	Abstracts	(Abstracts Involving Outpatients)
1969	2,077		931	
1970	2,341		996	
1971	2,219	(246)	991	(122)
1972	2,462	(411)	994	(168)
1973	2,360	(549)	1,175	(285)
1974	2,789	(786)	1,458	(402)
1975	2,993	(935)	1,510	(496)
1976	3,348	(1,120)	1,626	(661)
1977	3,282	(1,228)	1,752	(721)
1978	3,435	(1,130)	1,962	(743)
1979	3,500 est.	( )1/	2,200 est.	( )1/

1/ Outpatient publications not requested received a priority score between 201 and 250. Only 10 percent of the patient day usage was by investigators who received a priority of 255 or higher. The 90 percent usage by reviewed investigators whose projects received scores of 250 or better is very similar to the 95 percent recorded for funded NIH and NIMH R01 research grants in fiscal 1976. Analysis of the utilization of outpatient visits gave a similar result. Considering the difficulties involved in doing clinical research, and the importance of clinical trials, which generally receive lower priority scores because of lack of scientific novelty, this comparison suggests the work done on GCRCs is similar in scientific quality to that in the research grants program. A previous study established that the DRR site visitors award essentially the same average priority score (197) for protocols presented by grant-supported GCRC users as the DRG study section members do for these investigators' research grants in the same scientific areas (194), even though the study section score is not made known to the site visitors. The data from these sampling studies indicate that the quality of the work performed on the GCRCs is being effectively maintained by the national and institutional review systems.

Budgetary History

Table III describes a ten-year budgetary history of the program, showing the number of centers, positions and beds, and the appropriation. The inflationary factors in the program have been somewhat greater than those in the general economy during the past ten years. For example, the cost of personnel has increased at an annual rate of 9 percent per year for the past ten years, and is expected to continue at this rate at least through next year.

Hospitalization costs have increased at an even more rapid ratt, averaging over 13 percent. Between 1972 and 1977, these cost increases were somewhat ameliorated by recoveries from the service patient policy, but current analyses indicate that additional revenue from this source cannot be expected without substantially altering the program content and sacrificing program quality.

Typical GCRC

The budgetary makeup of a typical GCRC in 1980 is shown in Table IV.

Relationship of the GCRC Program to the NIH Clinical Research Program

Our analyses indicate that most of the investigators using General Clinical Research Centers are conducting studies sponsored under an NIH grant or contract. It seemed, therefore, of some interest to determine the geographic distribution of beds and outpatient resources in

TABLE III

GCRC PROGRAM, 1969 - 1981

FY	Centers	Positions FTE	Funded Beds	Apportionment (in thousands)
69	93	2,298	1,023	$ 35,004
70	93	2,076	904	35,004
71	82	1,885	881	38,004
72	84	1,867	907	42,181
73	83	1,790	893	41,300
74	87	1,795	877	42,320
75	84	1,732	823	42,619
76	84	1,727	784	42,533
77	82	1,679	755	47,283
78	79	1,706	633 1/	51,946
79	74	1,640	613 1/	51,941
80	75	1,687	600 1/	56,218 3/
81	71 2/			59,486 2/ 3/

1/ Excludes 73 beds used for C patients included prior to 1977
2/ Estimate
3/ Revised

TABLE IV

ESTIMATED AVERAGE CENTER

FUNDED FY 80

8.2 Beds

Personnel	FTE Positions	Dollars (thousands)	Dollar Totals
Professional	1.2	$59	
Administrative	1.5	23	
Laboratory	2.6	42	
Dietary	3.2	42	
Nursing	12.9	204	
Other 1/	.9	19	
Fringe Benefits	18.5%	72	$461.0
Hospitalization			
Routine		$225	
B 581 Pt Days x $151		(88)	
C 261 Pt Days x $151		(39)	
A 1686 Pt Days x $66 (ancillaries)		111	
Outpatient 1018 x 26		27	236.0
Travel			1.7
Supplies, Equipment, Other			35.0
			$733.7
Indirect Cost			49.0
			$782.7

1/ Includes 25.5 FTE Clinical Associate Physicians (CAPs) relation to the distribution of other grants and contracts for clinical research. The geographic distribution of GCRCs is shown in Figure I.

Unfortunately, there is currently no uniform definition for clinical research. Moreover, there are currently insufficient coded data on the contract program to permit computer retrieval and analysis. Since in 1978 contracts represented approximately 12 percent of NIH awards to medical schools, we felt omission of contracts would not seriously affect the study.

Because there is no uniform code for clinical research, we elected to study all grants which were coded for human subjects research and which were awarded to investigators with a Medical Doctorate (MD).[1] While we are aware that not all grants to MDs utilizing human subjects involve clinical research problems and that some grants to non-MDs would be considered clinical research, we felt that an analysis of HS grants to MDs would give us a reasonable approximation of the intensity and locations of clinical research activity.

We found that in 1979 there were 4376 grant awards totaling, $698.3 million, awarded by NIH to MDs in the U.S. for human subject (HS) research (Table V).[2] The 62 institutions which had 75 GCRCs in 1979 received 3144 of these grants, or 72 percent of the total awarded. Thirty-four institutions without GCRCs had ten or more HS grants totaling $96.0 million, while 203 institutions without GCRCs had from 1 to 9 HS grants awarded to MDs totaling $90.3 million.

We then grouped the HS awards to institutions which had GCRCs according to GCRC priority scores by quartiles (Table VI). It can be seen that the ratio of the mean NIH HSG to MDs dollars to mean GCRC dollars is slightly higher for the top quarter (11.1) of this program than the bottom quarter (7.3), but not strikingly so. Because of this relatively constant relationship, each GCRC award dollar serves nearly the same number of HS grants to MDs at institutions across the whole range of the GCRC program (Figure 2).

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[1] Grants prior to November 1975 were not coded for human subjects research. We estimate that 10 percent of the grants were missed in our search due to start dates prior to code initiation.

[2] A more recent preliminary analysis using the NIH Computerized Research Information of Scientific Programs (CRISP) system for 1979 identified 3693 grants totaling $686.6 million and 1327 contracts totaling $180.4 million as involving human subjects. In this analysis the total project was counted as HS research if any part of it involved human subjects

GENERAL CLINICAL RESEARCH CENTERS

FY 1980

Figure I

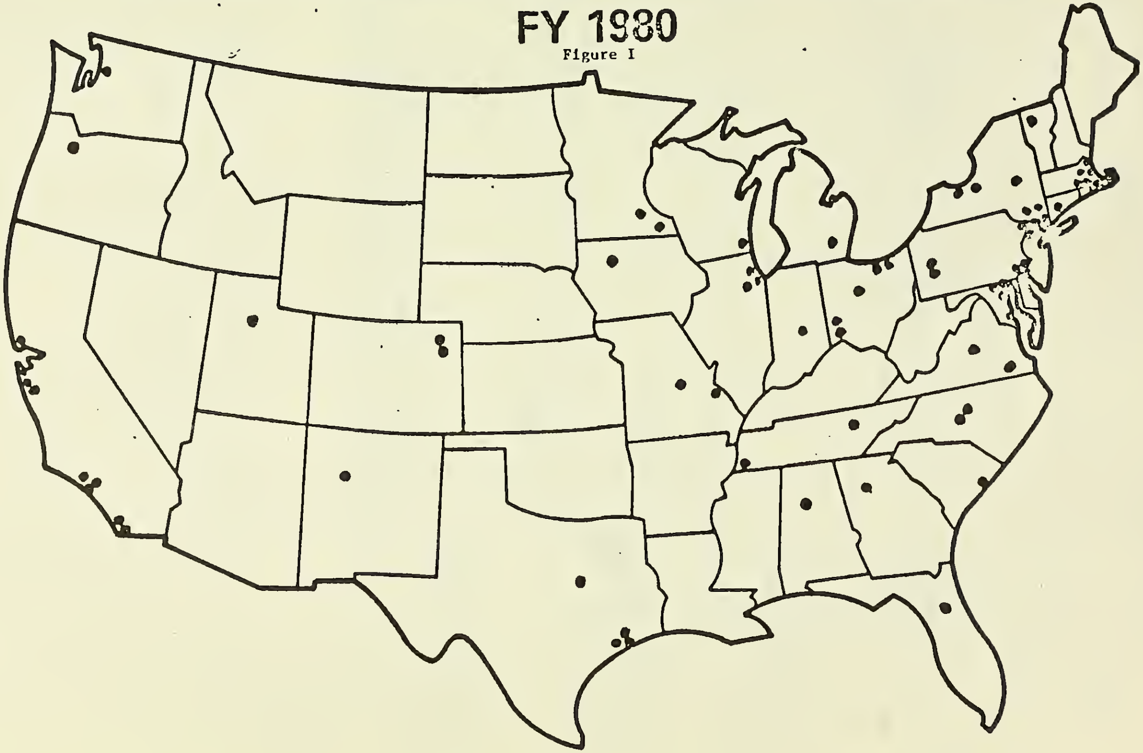


TABLE V

1979 DISTRIBUTION OF NIH HUMAN SUBJECT GRANTS (HSG) TO MDs BY INSTITUTION TYPES

	Institutions		HSGs to MDs		HSG Funds to MDs	
	Number	% of Total	Number	% of Total	$(Millions)	% of Total
HSG to MDs at Institutions with GCRCs	62	19	3144	72	508.7	73
HSG to MDs at Institutions without GCRCs but More than 9 HSG	34	10	566	13	96.0	14
HSG to MDs at Institutions without GCRCs and Less than 10 HSG	203	61	616	14	90.3	13
Total HSG to MD Foreign	33	10	50	1	3.3	1
Totals	332	100	4376	100	698.3	100

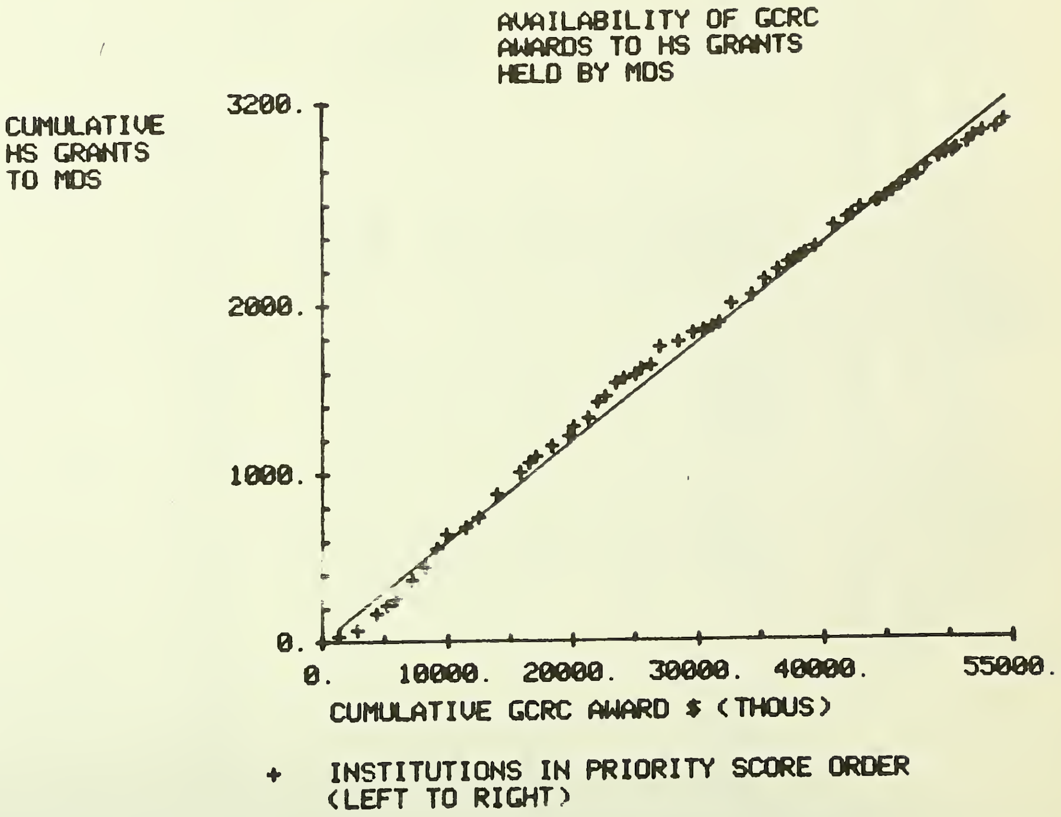
TABLE VI

CRC PROGRAM DIVIDED INTO QUARTILES BY PRIORITY SCORES SHOWING RELATIONSHIP OF NIH HUMAN SUBJECTS GRANTS (HSG) AWARDS DOLLARS TO GCRC DOLLARS AT 62 INSTITUTIONS WITH GCRCs

Quartile of Priority Scores	Rank of Centers Included*	Mean GCRC Award $/Yr (Thous)	Total NIH HSG Awards to MDs $/Yr (Thous)	Mean NIH HSG Awards to MDs $/Yr (Thous)	Ratio $ NIH/GCRC
First	1-16	1135.	201898.	12618.	11.1
Second	17-31	852.	108204.	7214.	8.5
Third	32-49	816.	125821.	7863.	9.6
Fourth	50-62	666.	72739.	4849.	7.3
			508662.		

*Inpatient centers only. Where there is more than one center at an Institution, priority scores were averaged.

Figure 2


AVAILABILITY OF GCRC
AWARDS TO HS GRANTS
HELD BY MDS
CUMULATIVE
HS GRANTS
TO MDS
3200.
2000.
1000.
0.
0.
10000.
20000.
30000.
40000.
55000.
CUMULATIVE GCRC AWARD $ (THOUS)
+ INSTITUTIONS IN PRIORITY SCORE ORDER
(LEFT TO RIGHT)

RESEARCH ACCOMPLISHMENTS

Urea Cycle Enzyme Deficiencies

A new therapy which promises to extend significantly the lives of infants stricken by previously fatal hereditary deficiencies of enzymes in the urea cycle involves the chemical stimulation of alternative pathways for the excretion of nitrogenous wastes. The treatment may be applicable not only to these rare disorders, but also to more common nitrogen-accumulating diseases such as Reye's syndrome, liver failure, and uremia. This work has also led to the important finding that the apparently asymptomatic carriers of a urea cycle disease called ornithine transcarbamylase deficiency, which is associated with severe mental retardation, may have subtle degrees of intellectual impairment.

Diabetes

New data indicate that physical training increases insulin binding and tissue sensitivity to insulin in proportion to the increase in physical fitness. A regular exercise program may therefore have an important role in the management of insulin resistant states.

A gene in the D region of the short arm of chromosome 6 is associated with a high incidence of susceptibility to diabetes. However, studies indicate that more than one gene is involved in susceptibility, and support the idea that a combination of genetic and environmental factors are involved in development of the disease.

Obesity

A possible biochemical explanation has been found for the tendency of people who lose weight to regain it. The enzyme lipoprotein lipase, which removes triglycerides from blood for storage in fat cells, increases to three or more times normal values in formerly obese people who have stabilized at a lower weight after stringent dieting. Enzyme levels seem to remain high as long as weight remains low.

Reye's Syndrome

A factor in the serum of patients with Reye's syndrome interferes with the proper functioning of mitochondria. The levels of the factor have important prognostic implications, as increases and decreases in the serum level are correlated with unfavorable and favorable outcomes respectively.

Alcoholism

Even mild levels of alcohol may result in significant degrees of demasculinization, including impotence and sterility. The sexual dysfunction seems to result from direct toxicity to the Leydig cells of the testes, which produce testosterone, and to sperm, as well as from damage to sections of the hypothalamus and pituitary controlling functions of the testes.

Infectious Disease

Investigations of a family with a sex-linked deficiency of a plasma membrane glycoprotein and a propensity to infection in the affected male members indicate impaired adhesiveness and chemotaxis by the white cells. These findings provide a new lead into understanding one of the body's primary defense mechanisms, the phagocytic leukocytes.

Hemochromatosis

Analysis of the gentotypes of relatives, as defined by HLA typing, together with tests of iron status, have made it possible to identify at an early age those heterozygous carriers of familial hemochromatosis who might have some biochemical expression of the disease and homozygotes who are destined to become clinically affected. The work has clarified the overall mode of inheritance of hemochromatosis and has offered new estimates of its frequency.

Menopausal Symptoms

Hot flashes experienced by post-menopausal women are caused by biochemical events in the brain, particularly sudden large releases of luteinizing hormone (LH) from the anterior pituitary. This suggests that LH, or more likely the factors that cause LH release, may trigger the hot flash. The perception of the hot flash results from sudden shift by the brain of the thermostat of the body, and the subsequent symptoms of perspiration and flushing are automatic cooling mechanisms. These findings suggest a new approach to therapy, involving the use of drugs called alpha-adrenergic inhibitors, which have been shown to block the release of LH in non-human primates.

Pituitary Tumors

Treatment with bromocriptine, an ergot alkaloid derivative, offers the first effective non-surgical therapy for two disorders caused by pituitary tumors, hyperprolactinemia and acromegaly. In hyperprolactinemia, now known to be much more common than previously thought, an excessive secretion of the hormone prolactin causes abnormal lactation, loss of menses, and sterility; bromocriptine lowers prolactin levels to normal and restores gonadal function. In acromegaly, the secretion of excess growth hormone causes coarsening of features, swelling of soft tissues, loss of gonadal function, and a tendency to diabetes; again bromocriptine helps reverse those abnormalities without adverse side effects.

Infant Epilepsy

A monitoring technique involving multiple methods, including electromyograms, electro-oculograms, electrocardiograms, respiration, and skin electrical responses has been developed to allow investigators to distinguish the serious disorder known as massive infantile spasms from other forms of epilepsy and from normal infant behavior. The method allows for the first time an objective evaluation of the possible efficacy of various drugs in this condition.

CLINFO

The CLINFO System, a computer-based data management system designed for clinical research applications, has been widely accepted by the clinical investigator community. The GCRC program continues to support the three prototype sites at the University of Washington, Baylor University, and Vanderbilt University. The production version of CLINFO, by Bolt, Beranek and Newman, Inc. of Boston, is expected to be installed on seven more centers by December, 1980. The centers where the production version has already been installed (Duke, Hopkins, and Cincinnati) are well satisfied with its operation and find that it is heavily used.

A GCRC Subcommittee on Data Management has been appointed to consider ways to satisfy the needs of GCRCs which desire some capability for data management, but on a lesser scale than the complete CLINFO System (Central Processor Unit, with 4-6 terminals and a System Manager). One of the alternatives under review is the new Digital Equipment Corporation's PDP - 11/23 computer, which is expected to accommodate the CLINFO software and up to two terminals; this configuration would result in appreciable savings. The extent of diffusion of CLINFO next year will depend on the competing priorities within the GCRC program in FY 1981.

A meeting of the System Managers (SMs) from the prototype sites and the seven newly awarded production sites was recently held. The new SMs found that this provided an excellent opportunity to learn from the experience of the prototype SMs. A SM Newsletter will be instituted with the help of Bolt, Beranek and Newman, and a Subcommittee of the SMs was formed to identify possible statistical capabilities that could be added via the "communication file" in the CLINFO System.

Clinical Associate Physician (CAP) Program

The CAP Program, a post fellowship program intended to develop clinical investigators and now in its seventh year, continues to attract candidates of high quality. The National Advisory Research Resources Council has approved two changes in the CAP Program: 1) future CAP applications and continuation requests may include an allowance of $5,000/year for small equipment, supplies, computer time, and travel (up to $800) to scientific meetings, and 2) each grantee institute will be permitted a maximum of two CAPs. If there are separate Adult and Pediatric Centers at a grantee institution (funded either separately or as a single grant) a maximum of three CAPs will be allowed. The salary remains at $30,000 per year. Forty-three CAPs are currently funded at a total cost of $1,382,206. This amount includes salary, fringe benefits, indirect cost, and allowance for equipment (for most recently funded CAPs). The GCRC Program plans to continue the CAP Program with special emphasis as a means of retaining talented young physicians in clinical research.

Clinical Trials

The program is currently undertaking a study of clinical trials through a contract awarded to the Rand Corporation entitled "The Evaluation of the Role of Clinical Research Centers in Clinical Trials, with Emphasis on Information Processing."

The goals of this contract are to: 1) determine how clinical trials of different sizes differ in methodology, computer requirements, and need for support personnel; 2) determine how clinical trials are designed and controlled; 3) evaluate the extent of collaboration, the difficulties (e.g., allowing investigators access to the compiled data base), and how these will impact on the clinical trials performed in CRCs; 4) characterize data management systems used in clinical trials at present, determine what problems are encountered in establishing such systems, and recommend how computer-based data systems can improve the format of a trial; and 5) determine the role of specific aids in administering clinical trials (e.g., keeping records, generating reports, admitting patients).

This contract will be completed in October, 1980, and a final report will be submitted. During the last year of the contract, the contractor interviewed approximately 200 investigators, program directors, nurses, dietitians, administrative coordinators, and other allied health personnel working on GCRCs and being involved in clinical trials. Efforts were mainly put in the area of examining the role of computer-based data management systems to support clinical trials which use GCRC resources and to compare CLINFO functionality and data capacity to the needs of those clinical trials. According to the modifications of the contract, less emphasis was put on the work tasks which dealt with cooperative efforts among investigators on different GCRCs, access to completed trials data bases, and establishing new data management systems for each trial.

Two presentations resulted from this contract. One entitled, "Trends in Clinical Trials Design", was presented to the Society for Clinical Trials, and one entitled, "Potential Roles for CLINFO and CLINFO Systems Managers in Clinical Trials using GCRC Resources" was presented at the CLINFO System Managers' meeting.

Division of Research Resources Five-Year Plan

In the development of the DRR five-year planning document, the following goals have been established for the GCRC Program:

- Emphasize continuation and promote growth of high quality inpatient and outpatient facilities for multidisciplinary clinical research.
- Provide and maintain mechanisms for developing and supporting clinical research manpower.
- Introduce and develop the placement of appropriate resource technologies for pursuit of clinical investigation.
- Establish administrative management objectives and follow-through for achieving 1) greater intra-institutional awareness of GCRC resources, 2) increased intra-agency coordination with categorical institute programs, and 3) improved operations and utilization of resources.
- Enhance the conduct of clinical trials in GCRCs.
- Expand the base of CLINFO installations to a minimum of two-thirds of the centers.

Administrative Coordinators

At the national meeting of the Administrative Coordinators a one day orientation was presented to new coordinators, in conjunction with the DRR Grants Management staff. Following this, during a day and a half meeting, the entire group reviewed areas involving the overall administration of the center grants.

Nurses and Dietitians

The National Association of Research Nurses and Dietitians, at its national business meeting, conducted a workshop to encourage communication between centers and help participants share problems and solutions unique to research centers. Continuing Education Unit Credits were given to members who attended the workshops.

Biomedical Research Support Program

The Biomedical Research Support Program administers two institutional research grant programs, the Biomedical Research Support Grant (BRSG) Program and the Biomedical Research Development Grant (BRDG) Program.

BIOMEDICAL RESEARCH SUPPORT GRANT PROGRAM

BRSG awards are made to institutions that receive each year at least three allowable Public Health Service (PHS) research grants totalling at least $200,000. The amount of each award is computed by a formula that is applied to the total dollar amount of allowable PHS research grants during the previous Federal fiscal year. BRSG funds are administered by each grantee institution where they are used for those direct costs of biomedical research that are not feasibly supported by other PHS research grants, or that are supported most effectively or at least cost with BRSG funds. The objectives of the program are to enhance the quality of biomedical research, increase its productivity, and reduce its cost.

The major plans identified in the DRR 5 Year Plan for the BRSG Program are:

1. Halt the persistent decline in the amount of BRSG funds, expressed as a percentage of total NIH research grant funds; and increase the percentage to 3.1 percent by 1986. The ultimate goal is to stabilize the BRSG funds at 4 percent, which is far below the statutory ceiling of 15 percent.
2. Halt the trend in which the decline in the amounts of BRSG awards is proportionally most severe for institutions with the largest amounts of PHS research grant support.
3. Develop more analytical measures to express the benefits of BRSG support.
4. Establish a shared instrument grant program in 1982.

A revised formula has been developed to accomplish item two of the 5 Year Plan. The proposed formula has the support of the General Research Support Review Committee and the NARRC. Final approval of the formula is expected in time for computation of the 1981 BRSG awards.

Regional meetings of program directors and BRS Program staff were held in Chicago in October 1979 and Ann Arbor in May 1980. There have been eight such meetings since they were initiated in 1978. Further meetings are being scheduled where none have yet been held.

A Guide to the Biomedical Research Support Grant Program has been prepared by the Research Resources Information Center. The guide describes the purposes, operation, and accomplishments of the program, and provides a list of institutions that received BRSG awards in 1980. Copies will be available for public distribution.

The following tables describe the utilization of BRSG funds, the amounts available, and their allocation to grantees.

TABLE I
FUNDING HISTORY
Biomedical Research Support (BRS) Program (Dollars in thousands)

	A	B	C	D
Year	Funds Available for NIH Research Grants 1/	BRS Authorization Ceiling (15% of Funds Available for NIH Research Grants)	BRS Appropriation	Column C as a Percent of Column A
1966	$ 604,377	$ 90,657	$ 45,200	7.5
1967	681,197	102,180	51,700	7.6
1968	727,366	109,105	59,700	8.2
1969	729,230	109,385	60,700	8.3
1970	744,061	111,609	57,677	7.8
1971	765,510	114,827	54,200	7.1
1972	901,119	135,168	55,212	6.1
1973	925,457 1/	138,818	60,700 2/	6.5
1974	997,878	149,681	45,149 3/	4.5
1975	1,142,783	171,417	42,957	3.7
1976	1,272,771	184,465	42,957	3.5
1977	1,419,821	212,973	40,873 4/	2.9
1978	1,610,036	241,505	40,873 4/	2.5
1979	1,868,551	280,282	45,021 4/	2.4
1980	2,117,695	317,654	47,516 4/	2.2

1/ Thru 1972 includes NIMH; 2/ Includes 33.5 million impounded funds;
3/ Excludes Minority Biomedical Support Program funds after 1973;
4/ Includes Biomedical Research Development Grant Funds

TABLE II
Distribution of BRSG Awards by Size

Size of BRSG Award (in thousands)	Number of Grantee Institutions				
	FY 1976	FY 1977	FY 1978	FY 1979	FY 1980
Under - $ 30.0	74	94	93	78	108
$ 30 - 49.9	87	89	89	93	89
50 - 99.9	116	115	106	105	101
100 - 149.9	60	69	79	82	102
150 - 199.9	48	37	30	41	106
200 - 249.9	19	51	48	58	--
250 - 299.9	37	--	--	--	--
TOTAL	441	455	445	457	506

Grant Range	Amount				
	FY 1976	FY 1977	FY 1978	FY 1979	FY 1980
Low	$ 17,418	15,565	14,198	14,441	13,449
High	261,305	213,709	200,462	201,413	189,787
Average	96,955	86,754	86,117	91,359	88,271

TABLE III
Total Entitlement* Compared to BRSG Funds Awarded

Fiscal Year	Entitlement*	BRSG Funds Awarded	Ratio BRSG/Entitlement
1976	$ 995,465,535	$42,957,000	4.32%
1977	1,060,171,080	39,473,000 1/	3.72
1978	1,153,259,633	38,322,272 1/	3.32
1979	1,324,013,741	41,751,118 1/	3.15
1980	1,619,308,880	44,654,213 1/2/	2.76

*Total allowable PHS grants used for computation of BRSG awards
1/ Excludes Biomedical Research Development Grant funds
2/ Excludes $400,000 for Minority High School Summer Research Apprenticeships.

TABLE IV
Distribution of BRSG Awards by Type of Institution

Type of Institution	FY 1973	FY 1974	FY 1975	FY 1976	FY 1977	FY 1978	FY 1979	FY 1980
Medicine	104	104	107	106	107	109	109	117
Dentistry	34	33	34	26	27	31	29	30
Osteopathy	0	0	1	1	1	1	1	1
Pub. Health	12	12	12	12	13	13	12	15
Pharmacy	14	12	17	13	14	12	13	20
Veterinary Med.	15	14	15	10	11	10	10	9
Nursing	3	4	5	3	2	4	5	3
Allied Health	1	1	1	0	0	0	0	0
Optometry	0	0	0	0	0	0	1	2
Hospitals	71	66	71	63	61	59	61	61
Health Dept.	2	2	2	2	1	1	2	2
Research Inst.	71	70	75	71	71	67	67	85
Other Academic 1/	113	108	121	134	147	138	147	161
TOTAL	440	426	461	441	455	445	457	506

1/ Academic institutions exclusive of health professional school components.

BRSG awards are used for a wide variety of purposes, some of which are illustrated by the following examples:

BRSG funds provided the original structure and definition for a pilot project at the State University of New York at Binghamton to understand the influence of alcohol on memory processing by humans. Investigators are testing hypothetical interactions between the influence of alcohol and the determinants of memory processing by humans: original strength of the acquired memory, quality of the processing, or circumstances of memory retrieval. Based on their BRSG pilot data, the investigators have now obtained an NIAAA multi-year grant to continue the research.

The BRSG-funded work of an investigator at the University of Tennessee, Knoxville, relates to a question of animal biology--but the findings may eventually lead to the alleviation of certain human diseases. The experiment with marmosets have showed that fetal hemoglobin can be reactivated in the adult bloodstream, opening the possibility that a particular type of hemoglobin made by an individual suffering from a blood disease such as sickle cell anemia can be induced to cease functioning and another type "turned on" to take its place, relieving some of the diseases' painful crises.

At the University of Florida, BRSG funds have been combined with funds from NSF and the University's College of Engineering to purchase an image processing system to automate measurements from ultra high-speed laryngeal films. "Equipment dollars are hard to come by," said the principal investigator, "and the BRSG enabled us to pool money from several sources to obtain a vital piece of equipment." This study concerns a theory of laryngeal vibratory motion and the role vocal cord motion plays in the production of vocal sound. Two applications of the work are the detection of laryngeal disorders and the development of aids for the hearing-impaired to learn to speak more naturally.

BIOMEDICAL RESEARCH DEVELOPMENT GRANT PROGRAM

The BRDG Program is a competitive institutional grant program intended for institutions that have limited health research capability, have significant health manpower training responsibility, are committed to improving and sustaining their health-related research, and offer strong potential for high quality health-related research. The objective is to strengthen and/or expand health-related research in eligible institutions provided it will result in improving the training of manpower for clinical health professions or health-related research or both.

Ten new BRDG awards were made in 1980. The new and continuation 1980 awards total $2,841,787. Twelve BRDG awards terminated in 1980 after three years of continued support. As stated in the annual report last year, no more new awards will be made after 1980. The final continuation grants will be awarded in 1982. Eleven types of institutions have received BRDG awards since the program was begun in 1977.

TABLE V
BRDG AWARDS SINCE 1977

School of Medicine	9
School of Dentistry	3
School of Osteopathy	3
School of Pharmacy	7
School of Veterinary Medicine	5
School of Nursing	2
School of Podiatry	1
School of Optometry	1
Other Academic	4
Hospital	3
Research Organization	4
	42

After two full years of BRDG support, eight of the original twelve grantee institutions had developed Public Health Service research grant support sufficient to receive a Biomedical Research Support Grant (at least three PHS research grants that total $200,000 or more). The attraction of research grant support by the original tweleve grantee institutions is shown in the following table.

TABLE VI
RESEARCH GRANT SUPPORT
ORIGINAL TWELVE BRDG GRANTEE INSTITUTIONS
AS OF 9/77 AND 7/79

Funding Source	9/77	7/79
Public Health Service		
NIH	$437,944	$4,882,690
ADAHMA	171,021	892,314
HRA		9,660
Other Federal		
NSF, NASA, USDA, RDA, VA, OTHER	180,466	1,064,456
State	5,050	120,000
Private	112,283	818,643
	$906,764	$7,787,763

Plans are being developed to evaluate the BRDG Program. The evaluation will determine whether or not significant and long lasting improvement occurred in the biomedical research capabilities of the grantee institutions, and the role of BRDG support in those improvements. The level and duration of the grants, and the uses of the grant funds will be evaluated.

GENERAL RESPONSIBILITY

The Minority Biomedical Support (MBS) Program is charged with the responsibility of trying to rectify the problem of the underrepresentation of ethnic minorities in biomedical sciences. Resolution of this problem is approached through the granting of institutional awards focused on providing minorities equality of opportunity to engage in biomedical research. The MBS Program supports projects designed to strengthen biomedical research capabilities of institutions with a significant commitment to minorities, and to increase and expand the involvement of faculty and students in biomedical research.

SPECIFIC OBJECTIVES

The overall mission of the MBS Program is necessary as a result of the dearth of minority scientists. Therefore, the specific objectives of the Program are:

a. to increase the numbers and quality of minority biomedical scientists,

b. to strengthen and develop the research setting (eligible institution) in which biomedical research can be conducted, and

c. to broaden the opportunities for involvement in biomedical research by ethnic minority faculty, students and investigators.

The MBS Program provides funds for released time so that faculty may have the opportunity to conduct biomedically oriented research. Equipment, supplies and necessary renovations for approved research projects are supported by this Program. In addition, funds are provided for student participation in research as well as for consortia, collaborative arrangements, special summer projects, and travel to scientific meetings.

In June 1974, the Director of the National Institutes of Health requested that all Bureaus, Institutes and Divisions initiate and coordinate their minority programs activities through the existing minority programs (i.e., Minority Access to Research Careers Program (MARC), (NIGMS), and the MBS Program, DRR. It is through this mechanism that the Intra-Agency Agreements between the Institutes and the MBS Program were forged. Intra-Agency Agreements provide for the transfer of funds from one Institute to another for the purpose of supporting elements in the programs of the receiving institution. In this manner, the Institutes' at NIH can identify MBS subprojects that fit within the scope of the institutes mission and funds are transferred to DRR for support of the projects through the MBS grants.

The purpose of the Intra-Agency Agreements are to place Minority Biomedical Support (MBS) Program investigators in a position to enter the research arena of the cooperating Institute. Via the cooperating agreement, investigators are made more aware of the Institute's research thrust and application requirements and likewise the BID staff become familiar with this emerging talent pool of biomedical researchers.

GROWTH AND SCOPE OF THE PROGRAM

The Program awarded the first grants to 38 institutions in 1972 with a budget of $2 million. The number of grantees has increased to 79 in 1980 with an appropriation of $18.089 million. Included in the appropriation since 1979, is an increase of about $4 million for payment of indirect costs. The grantee institutions had been subsidizing the indirect costs until fiscal year 1979 when the Congress approved and appropriated funds for payment of indirect costs.

Reimbursements (funding of projects) through Intra-Agency Agreements increased from $342,000 in FY 1975 to about $6,035,756 in FY 1980. There has been an increase in the number of projects supported by other Institutes from 8 in FY 1975 to 129 in FY 1980.

With exception of the National Institute of General Medical Sciences and the National Institute of Environmental Health Sciences, all of the Institutes of the National Institutes of Health and the National Institute of Mental Health are participating in these cooperative agreements.

ADMINISTRATIVE ACTIONS

Grantsmanship Workshops

As part of the Program goals to develop faculty and institutional capabilities to engage in biomedical research, the Branch planned and sponsored four grantsmanship workshops during FY 1980. Part of the thrust was to encourage and assist faculty in the social and behavioral sciences as well as the biomedical sciences to write research proposals that would be submitted as components of MBS applications as well as individual grant applications submitted through other channels. Staff recognized the need to provide technical assistance to faculty from minority institutions in preparing high quality research grant applications to improve their competitiveness in the Peer Review process. Several staff members from other elements of the NIH were utilized in the workshops. An agendum was developed along the lines of a mini-course involving at least two NIH staff with each small group of 10-15. The schedule included illustrated lectures on: (1) "Common Problems and Deficiencies Encountered in Research Grant Applications," (2) "Development of a Typical Research Grant Budget", (3) "Understanding the NIH Peer Review Process", and (4) "Overview of NIH Grant Programs".

Each lecture was followed up with small workgroup sessions that examined typical research grant applications selected or designed specifically for the topic to be discussed. Actual hands-on experience in critiquing each portion of an application was provided in the small groups as well as an exercise to develop a budget for a mock application. The objectives and general agenda are included as Appendix A. Initially, the planning included 5 regional workshops. However, due to travel restrictions and other staff commitments, only four were conducted. A total of about 310 faculty members from MBS grantee institutions participated in the four workshops. The participation was limited to those faculty who had little or no experience in writing research grant proposals or who had been unsuccessful in previous MBS applications. At least one grants officer from each institution also was invited to participate.

Five-Year-Plan

Development of the MBS portion of the DRR Five-Year-Plan was initiated during FY 1979 and was completed during FY 1980. The process involved staff, the Program Advisory Committee and Council workgroups in identifying and prioritizing the future needs and directions of the Program. The planned actions in the three thrusts of the Program were:

1. Student development would involve initiatives to establish predoctoral fellowships, undergraduate summer training away from the parent institution, and coordination with the Department of Education's Biomedical Program to provide summer enrichment opportunities to high school students.

2. Faculty development would emphasize a quick turn around review for short term postdoctoral awards for retraining in special areas. A second initiative for faculty would implement a longer term award such as a research career development award.

3. Institutional development initiatives included visiting consultants for periods of two weeks to two years, facilities development awards as a one-time award for central resources, and establishment of institutional awards to undergraduate women's colleges on a similar approach as the present MBS Program.

Also identified in the Five Year Plan is an overall evaluation for the MBS Program to be launched in 1982.

Collaborative Activities with Other DRR Programs

An agreement was established between the MBS Program and the Biotechnology Resources Program whereby some MBS grantees would be identified as potential users of the PROPHET system. The Biotechnology Resources Program set up demonstrations at the MBS Program Directors Meeting in December 1979 and during the Annual MBS Symposium in April 1980. As a result of the demonstrations and other staff efforts, four MBS grantee institutions submitted proposals for consideration as PROPHET user sites. It is anticipated that all four will be approved and established early in FY 1981.

Another collaborative effort was initiated between the MBS Program and the General Clinical Research Centers (GCRC) Program in assisting with preparation of an application from Meharry Medical College for a MBS grant to develop the clinical research capability of that medical school. If the application is approved and funded, it would assist the institution in developing the capacity to compete for a GCRC after the initial MBS award. The award would involve co-funding by the MBS and GCRC Programs.

Revision of Policy and Information Statement

The MBS Program Policy and Information Statement was revised and reviewed by program directors and published as an interim version. Included in the policies are newly approved criteria and guidelines for the review committee to use in evaluating investigators, taking into account the variety of institutions in which they are situated. These guidelines will also assist NIH staff in making funding decisions. A copy of the document is attached as Appendix B.

Expansion of the Program

There was an increase in the MBS appropriation for FY 1980 and a mandate from the Congress to expand the Program to institutions not previously participating. Announcements went to all institutions identified as being eligible. Several new applications were received and eight of them were approved and funded during FY 1980, thus expanding the grantee community to 79. Additional expansion occurred by soliciting supplemental applications that included investigators in the social and behavioral sciences. These increased the participation of the National Institute of Mental Health, the National Institute of Child Health and Human Development, and the National Institute on Aging through the Intra-Agency Agreements.

ACCOMPLISHMENTS

Student Participants

In FY 1980 there were 1,027 undergraduates that participated in the Program. The 44 institutions, whose annual reports have been received, reported that 302 MBS students received B.S. degrees. The career choice for the 302 MBS graduates were: 68 admitted to medical school, 27 to dental school, 80 to graduate school, 57 to other health related careers. All MBS graduates from MBS-supported junior colleges transferred to 4-year colleges.

The 302 students also accounted for 300 papers presented at scientific meetings.

The comparable data for FY 1979 which are now complete for 68 institutions that reported are as follows:

1. Total student papers presented - 550,
2. Total MBS graduates (B.S. degree) - 443,
3. Career choices were: 133 to medical school, 118 to graduate school, 21 to dental school, and 118 to other health careers.

The graduate student participants in FY 1980 numbered 372. An estimated 10-15 Ph.D.'s will have been completed by MBS graduate students this year. Only 10 of the 79 MBS grantee institutions have Ph.D. programs. This will bring up to nearly 50 Ph.D.'s awarded to MBS graduate students at MBS institutions since the program started. An estimated 100 MBS graduate students completed master's degrees in FY 1980 most of these are continuing predoctoral training.

Faculty participants

There are 660 faculty members participating in 480 projects as of the end of FY 1980. The 44 institutions that have submitted progress reports to date indicate that these faculty have made 152 presentations at scientific meetings and published 167 papers in refereed journals. Similar data for the previous year (1978) included 315 publications and 320 presentations.

About thirty current or former MBS faculty participants are currently members of NIH study sections, advisory committees and Councils. This represents almost a doubling of the number in the past two years.

Annual MBS Symposium

The Eighth Annual MBS Symposium was sponsored by the Atlanta University Center in April 1980. About 1,400 participants attended. This year the poster sesssion was expanded to 251 and more students were able to present their research results during the meeting. Several workshops on use of computers and various new research techniques were held for participants. Among the 230 papers presented, were invited presentations by two Nobel laureates and several other well known biomedical scientists. More than 50 graduate and health professional schools had booths for recruiting minority students.

Applications for sponsoring the symposium, in future years, were solicited and three were received and reviewed. The annual symposium will be held in Albuquerque, New Mexico in FY 1981 and 1982.

Minority Biomedical Support Program
Division of Research Resources
National Institutes of Health
Bethesda, Maryland 20205

MBS Grantsmanship Workshops (1980)

OBJECTIVES

A series of five NIH-sponsored regional grantsmanship workshops designed to improve the quality of research grant applications submitted by minority faculty and others who serve (teach/train) large numbers of minorities is proposed. It is expected that this activity will result in more competitive research grant applications submitted to NIH and other Federal and non-Federal funding sources. In addition, the material developed from the workshops is expected to serve as a prototype for bringing minority individuals into the mainstream of Federal funding sources. Workshop participants will be selected from the institutions funded through the Minority Biomedical Support (MBS) Program of the Division of Research Resources (DRR) of the National Institutes of Health (NIH). The MBS Program seeks to increase the number of minority individuals engaged in biomedical research and serves predominantly minority institutions and those institutions with substantial minority student enrollments.

Travel and per diem will be provided for 3 to 5 biomedical science faculty from each MBS grantee institution. Each participant selected should be a full-time faculty member in the natural, behavioral or social sciences, and should have an interest in and the potential for writing a biomedically related research grant. Each participant is expected to disseminate the information/skills obtained to other faculty at his/her home institution.

ACTIVITIES

Major activities include the following:

- the discussion of the common problems and deficiencies encountered in some research grant applications,
- the discussion and critique of a typical research grant application,
- the development of a typical research grant budget and a discussion of associated pitfalls,
- presentations indicating the aspects of successful grantsmanship,
- presentations on the NIH peer review process for research grant applications,
- an overview of NIH programs and introduction of participants to key NIH program managers.

Upon completion of the workshop activities each participant should:

- be able to develop and write a well organized research plan following the revised Form 398 Instructions for NIH Grant Applications,
- be able to develop an appropriate budget for a research grant application,
- understand the peer review process of the NIH,
- have some knowledge about the mission structure and resources of the NIH in order to know where and from whom to get help in developing a research grant proposal.

EXPECTED OUTCOMES

The NIH-sponsored grantsmanship workshops are expected to:

a. produce a pool of 200-300 individuals well trained in grantsmanship skills at predominantly minority institutions and those institutions that serve large numbers of minorities.

b. increase the number of applications for NIH grants from investigators at these target institutions.

c. act as a multiplier in increasing the number of faculty at the target institutions with sharpened grantsmanship skills, through seminars/discussions by the initial 200-300 individuals at their home institutions.

d. increase the competitiveness of proposals from faculty from the targeted institutions.

e. ultimately increase the percentage of Federal and non-Federal R&D funds going to the targeted institutions.

EVALUATION/EVOLUTION

The overall success of the workshops can only be measured in terms of how successful faculty at targeted institutions are in obtaining grant funds over a period of years. This type of protracted indicator is of limited value in evolving the best prototype for training minority faculty in grantsmanship. Although, we feel that the typical workshop format described in the attachment contains the basic elements for developing successful grantsmanship, it is likely that certain components of the workshops need more emphasis than others and that we have overlooked other components which are vital to the success of being successful grantspersons at the targeted institutions. In order to have the program evolve and become more focused each participant will be asked to rate the various components of the workshop based on importance to him/her in sharpening grant acquisition skills. They will also be asked to suggest components which should be added and/or deleted.

Every attempt will be made to incorporate the suggested changes for each subsequent workshop. Therefore, the workshop content should evolve into a sharply focused prototype based on input from the 200-300 participating scientists.

The fate of research grant applications submitted to NIH by each participant and his/her colleagues at the home institution will be monitored to determine whether there is an increase in the number approved and an increase in the number funded.

Criteria for Evaluating Competing Applications; Levels of Continued Support

The major objective of the MBS Program is to increase the numbers of minority journeymen biomedical researchers. It is also important to emphasize the role of student participants in the research projects.

The present authority for the MBS Program is through Section 301 of the PHS Act as amended. This authority is to fund research and not training. It is, therefore, implicit that the emphasis of the program be scientifically meritorious research projects that involve students as participants in an apprenticeship or on the job experience.

Applications and Funding

The make up of an application must involve research projects with scientific merit as judged by peers in the respective scientific disciplines. Each research project must, therefore, be assigned a priority score on the basis of scientific merit. Appropriate strengths and weaknesses for both scientific merit and student participation (MBS goals) should be developed for each project.

Regardless of all other factors, research projects must be meritorious in order to be supported by the MBS Program. Merit will be determined by the Peer Review process and the level of support for each investigator will also depend on the institutional capabilities and environment.

How are investigators from different types of institutions evaluated, and for how long should they receive MBS support? In evaluating each investigator, it is important to sort out the institutional environment. The MBS grantee institutions offer a variety of environments for carrying out the goals of the programs, ranging from two year colleges to institutions with Ph.D. programs and health professional schools. Therefore, the expectations for investigators in a small undergraduate college or two year college cannot be the same as for those in an institution that awards Ph.D., M.S. and/or Health Professional degrees.

Institutions with graduate programs normally expect their faculty to conduct research as part of their institutional duties. It is anticipated that the institution can provide some support and release time for their research. However, where the support is justifiably inadequate the MBS Program can provide them with some support to carry out MBS goals.

Renewals (Competing Continuations)

Generally, each investigator should expect to be evaluated for scientific merit and productivity, as measured by peers in his/her particular area of expertise. The measures of productivity are publications in refereed journals, presentations at scientific meetings, research grant applications submitted and obtained, and the success of students who have participated in the research in pursuing careers in biomedical sciences.

After an initial grant, investigators at graduate and professional schools should show productivity other than training students. MBS support to such investigators should be sufficient to initiate the project and carry it out to completion. Future support should not have to be at the same level as a previous grant period, but should be expected to diminish as other sources of support begin to flow to the investigator. Support for students, however, would still continue as justified. Future levels of support should be dependent on evidence of efforts to gain other support and productivity.

On the other hand, an investigator at a small undergraduate college, of necessity, must continue to spend a great deal of the time teaching. Therefore, there is a need to continue adequate, but limited, support for a research project as long as the research is scientifically meritorious. Supporting an investigator for the sake of "training" students solely is not within the scope of the MBS Program. The scientific research project must first be judged as meritorious, then the student involvement considered.

In competing for an MBS award, each investigator will, by definition, be reviewed as a new, inactive or active investigator. Upon receipt of an MBS award, each investigator in each category accepts the responsibility of working toward the anticipated productivity outlined in Table II. Investigators who fail to meet the expected outcomes following participation in the MBS Program should be advised by their program directors (in advance) that their subsequent projects may be disapproved.

Recommended Criteria

There is a need for establishing different levels of support for the various classes of investigators, taking into account the home institution, length of previous MBS support, and efforts at productivity.

A guide for comparing MBS support for investigators at different levels of development and at different institutions is included in the attached tables.

These criteria can be helpful in the review of new applications, and also evaluating renewals (competing continuations) and non-competing continuations. They can also be helpful to staff at the time of making funding decisions.

Table I

Expectations of Institutions Accepting MBS Support

Institution	Expected Outcomes
2 year colleges	o Introduction of students to biomedical research; successful transfer of students to 4 year institutions; continuation of career development in the biomedical sciences for both faculty and students. o Faculty should show productive involvement in biomedical research commensurate with the environment (See Table II)
4 year colleges (excluding those with doctoral programs)	o Successful development of faculty involvement in biomedical research. o Institutional support of biomedical research activities and the creation of a competitive research environment. o Minority students having completed degree programs at all levels which involve biomedical research. o Minority student participants on the MBS Program continuing on to pursue advanced study and participation in biomedical research.
Institutions with doctoral programs	Same as for 4 year colleges plus the following: o Production of new knowledge from basic and/or clinical research in biomedical sciences. o Production of minority investigators at the doctoral and post-doctoral levels, o Maintenance of a scholarly and productive environment in biomedical sciences. o Career advancement for existing minority faculty scientists.

Types of Support and Relative Expectations for MBS Investigators Table II

Type of Investigator	Type of Support Through MBS	Expected Duration Years	Expected Outcome
New	Regular Grant--MBS Project support equipment, supplies, consultantsm technician(s), student research participants, etc.	3-6	a) One to several publications b) One or more research grant applications submitted c) One or more non-MBS research grants funded d) Increased focus in biomedical research area e) Several minority students trained and graduated f) Movement of the investigator into the active category
Inactive	A. Support for renewal or refocusing of research career	1-2	a) Rejuvenated researchers with a sharply focused interest in a biomedical science area b) Evidence of efforts to publish results of research c) Evidence of effort to obtain a non-MBS research grant
	B. Regular MBS Project Support	2-6	Same as a-f under new investigator
Active	A. Restricted MBS Project support (Minor equipment, supplies, consultants. Major emphasis will be on student support; technical support where justified)	Indefinite but on a 3 year funding cycle	a) Several minority students trained and possibly graduated b) Continued research grant applications to non-MBS sources c) Continued and increased publication rate, especially where technical support is provided.
	B. Pilot Project--limited equipment, limited personnel	1-2	a) Completed feasibility study b) Preliminary data acquired c) Applications submitted to non-MBS external funding agencies for research support.
	C. Major Equipment--Partial or full	Once	a) Investigator at a minority institution with state-of-the-art equipment

An individual investigator could conceivably start in the MBS Program as a new or inactive researcher and advance with program support to active status and still continue to receive some level of support

New Investigator - an individual who has received the Ph.D. or completed postdoctoral research within the past 2 years.

Inactive - an individual who has not held a sponsored research grant during the previous 3-5 years and does not qualify as a new investigator

Active - an individual who is presently productively engaged in research and does not qualify under the above categories.

The Office of Grants and Contracts Management (OGCM) staff played an important role in the review, negotiation, award making, and the administration of the ongoing grant programs, as well as aiding in the administration of contracts that are made by the Research Contracts Branch, Division of Contracts and Grants. During FY 1980, a total of 854 grant awards in the amount of $166,551,000 and 3 new and 26 contract modifications in the amount of $4,559,000 were made.

There was a substantial increase in the intra-agency activity for the Minority Biomedical Support program. In FY 1980, a total of $6,035,756 was funded by NIH Institutes and NIMH. This is an increase of 31% over FY 1979. This activity resulted in a large workload increase for the OGCM staff.

The following tables and charts reflect the DRR grant and contract effort for FY 1980. Particular attention is invited to the chart titled "DRR Research Grant Awards Fiscal Years 1970-1980 Constant/Current Dollars." In FY 1980, DRR's constant dollars for research grants continued to decrease. It is assumed that in FY 1980 all I/Ds except DRR will continue to show increases in constant dollars for research grants.

DIVISION OF RESEARCH RESOURCES
FY 1980 OVERVIEW OF GRANT AND R&D CONTRACT PROGRAMS (Estimated)

Program	Funding	Major Resources Supported
General Clinical Research Centers Program	$ 56,335,000	● 76 General Clinical Research Centers (Includes one phase out) ● Over 2900 Research Projects ● 45 Clinical Associate Physicians
Biotechnology Resources Program	$ 17,561,000[1]	● 45 Biotechnology Resources __ 18 Computer Resources (4 contracts) __ 2 Biomedical Engineering Resources __ 24 Instruments for Biological Structure and Function __ 1 Cellular and Biochemical Material Resource
Animal Resources Program	$ 24,569,000	● 7 Primate Research Centers, including 220 Core Research Projects ● 8 Primate Breeding Projects 69 Animal Research and Resource Project Grants and Contracts ● Training Programs
Minority Biomedical Support Program	$ 23,925,000[2]	● 79 Institutions ● 480 Research Projects ● 660 Minority Faculty, 1,027 Undergraduates, and 302 Graduate Students ● Minority Symposium
Biomedical Research Support Program	$ 47,896,000[3]	● Biomedical Research Support Grants to 506 Institutions ● 10,000 Pilot Research/Regular Research Projects ● Central Resources ● Development Awards to 30 Institutions
Office of the Director	$ 824,000[4]	● Culture Collection and Research Resources Reporter Contracts
Total Funding	$171,110,000	

1/ Includes $ 807,000 other than DRR appropriated funds
2/ Includes 6,036,000 " " " " "
3/ Includes 380,000 " " " " "
4/ Includes 588,000 " " " " "
$7,811,000

DRR FY 1980 GRANT AND R&D CONTRACT AWARDS BY MECHANISM (Estimated)

(Dollars in Thousands)

PROGRAM ACTIVITY	Research Grants: Research Centers Type	Research Centers No.	Research Centers Amount	Research Grants: Other Research Type	Other Research No.	Other Research Amount	Training Programs Type	Training Programs No.	Training Programs Amount	Res. & Develop. Contracts Type	Res. & Develop. Contracts No.	Res. & Develop. Contracts Amount
General Clinical Research Centers Program..........		M01s										
	2	23	$15,494	1	1	$ 68				New		--
	3	21	1,541							Mod.	2	$ 106
	5	53	39,126									
		97	$56,161									
Biotechnology Resources Program..................		P41s			R24s							
	1	4	$ 1,817	2	2	$ 874				New		--
	2	10	2,458	3	2	179				Mod.	9	$2,323 1/
	3	7	498	5	1	436						
	5	23	8,976									
		44	$13,749		5	$1,489						
Laboratory Animal Sciences and Primate Research Program..................		P40s			R24s			F32s				
	1	8	$ 1,087	1	3	$ 158	5	1	$ 21	New	3	$ 315
	2	7	1,349	2	2	67				Mod.	13	991
	3	9	122	3	1	27					16	$1,306
	5	29	3,443	5	4	184						
		53	$ 6,001		10	$ 436						
		P51s			K04s			T32s				
	2	1	$ 2,130	5	1	$ 39	2	2	$ 114			
	5	6	14,001				5	6	508			
		7	$16,131					8	$ 622			
								T35s				
							1	1	$ 13			

OGCM FY-1980

DRR FY 1980 GRANT AND R&D CONTRACT AWARDS BY MECHANISM (CONTD)

(Dollars in Thousands)

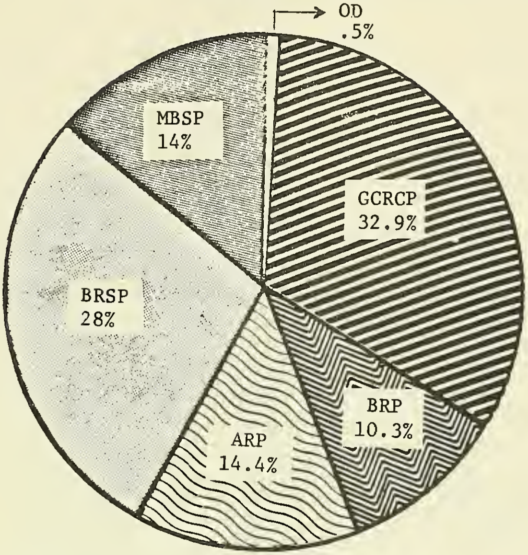
PROGRAM ACTIVITY	Research Grants: Research Centers Type	Research Grants: Research Centers No.	Research Grants: Research Centers Amount	Research Grants: Other Research Type	Research Grants: Other Research No.	Research Grants: Other Research Amount	Training Programs Type	Training Programs No.	Training Programs Amount	Res. & Develop. Contracts Type	Res. & Develop. Contracts No.	Res. & Develop. Contracts Amount
Biomedical Research Support Program..........					S07s							
				1	44	$ 1,408						
				2	462	43,646						
					506	$45,054 2/						
					S08s							
				1	10	$ 1,249						
				5	20	1,593						
					30	$ 2,842						
Minority Biomedical Support Program..........					S06s							
				1	8	$ 2,019						
				2	31	12,233						
				3	11	531						
				5	39	9,086						
					89	$23,869 3/						
					R13							
				1	1	$ 56						
Office of the Director...										New		--
										Mod.	2	$ 824 4/
TOTAL		201	$92,042		643	$73,853		10	$ 656		29	$4,559

NOTE: EXCLUDES SCIENTIFIC EVALUATION GRANTS

1/	Includes $	807	other than DRR appropriated funds
2/	Includes	380	" " " " "
3/	Includes	6,036	" " " " "
4/	Includes	588	" " " " "
		$7,811	

FY 1980* AWARDS BY DRR COMPONENT

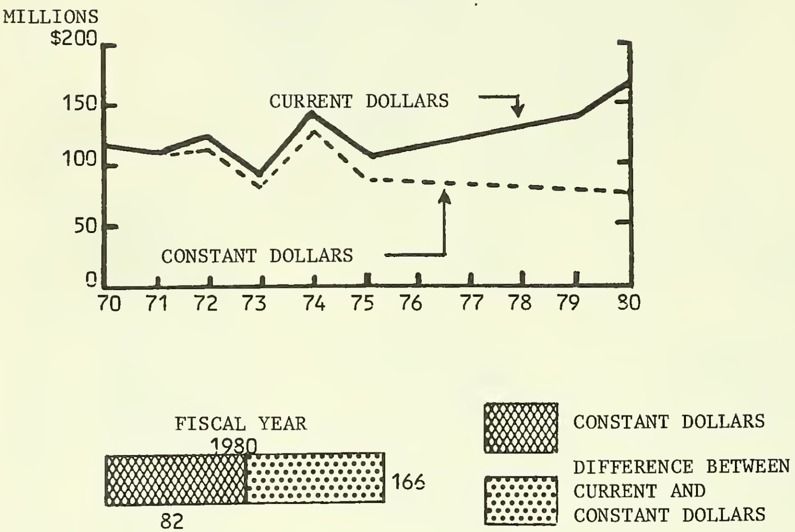
(INCLUDES RESEARCH GRANTS, RESEARCH TRAINING GRANTS, AND R&D CONTRACTS)



General Clincal Research Centers Program	Research Centers	$ 56,161,000
	Other Research	68,000
	Contracts	106,000
		$ 56,335,000 (32.9%)
Biotechnology Resources Program	Research Centers	$ 13,749,000
	Other Research	1,489,000
	Contracts	2,323,000
		$ 17,561,000 (10.3%)
Animal Resources Program	Research Centers	$ 22,132,000
	Other Research	475,000
	Training	656,000
	Contracts	1,306,000
		$ 24,569,000 (14.4%)
Minority Biomedical Support Program	Other Research	$ 23,925,000 (14%)
Biomedical Research Support Program	Other Research	$ 47,896,000 (28%)
Office of the Director	Contracts	$ 824,000 (.5%)

*Estimated

DRR RESEARCH GRANT AWARDS
FISCAL YEARS 1970-1980*
CONSTANT/CURRENT DOLLARS



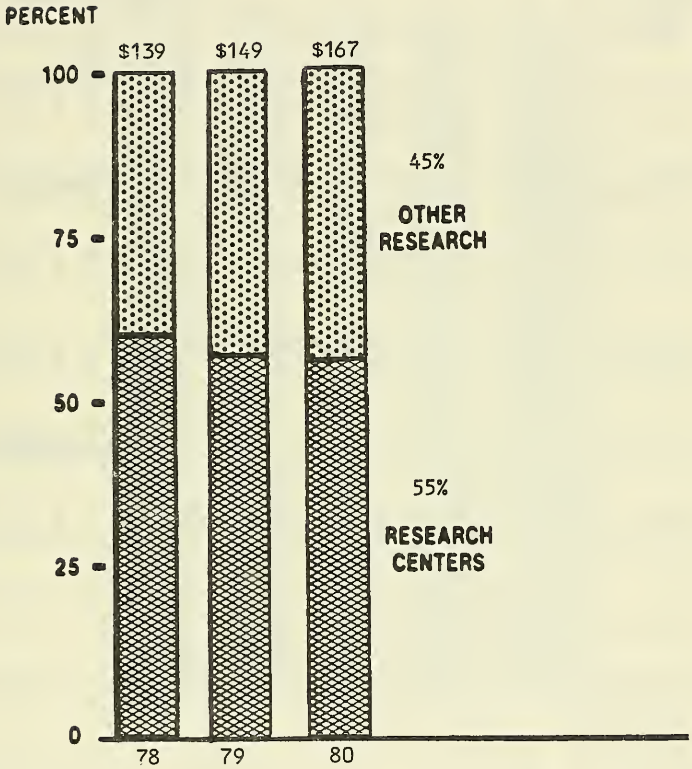
NOTE: BASED ON BIOMEDICAL R&D PRICE DEFLATOR FY 1970=100

SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH

*1980 ESTIMATED

DISTRIBUTION OF DRR RESEARCH CENTER AND OTHER RESEARCH GRANTS
FISCAL YEARS 1978-1980*

(DOLLARS IN MILLIONS)

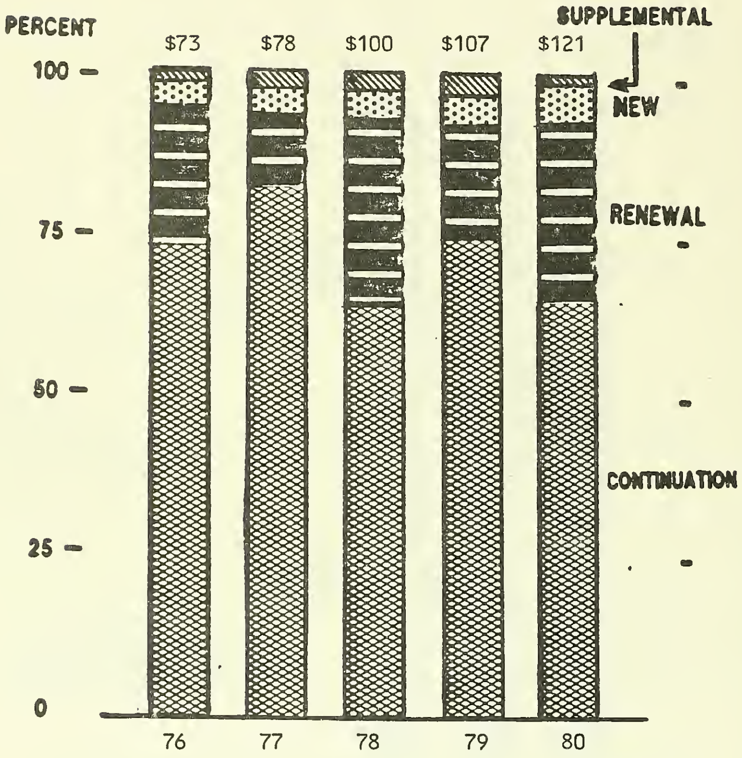


NOTE: SCIENTIFIC EVALUATION GRANTS ARE EXCLUDED

*1980 ESTIMATED

DRR RESEARCH GRANTS BY TYPE
FISCAL YEARS 1976-1980*

(PERCENT OF AMOUNT AWARDED; DOLLARS IN MILLIONS)



NOTE: EXCLUDES BRS AWARDS

*1980 Estimated

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A Letter From the Director

Joe R. Held, D.V.M., Director
Division of Research Services
National Institutes of Health

Those of us responsible for providing the essential services that support biomedical research face a continuing challenge in coping with the relative declines in available resources. Simply put, we must be constantly searching for ways to increase the efficiency and effectiveness of our services so the high quality of biomedical research at NIH will be maintained.

An illustration of this process can be found in the essay by Walter S. Friauf of the Division's Biomedical Engineering and Instrumentation Branch (BEIB) on page 9 of this report. He tells how a careful analysis of the requirements of an investigator in conducting an experiment may yield major savings in time and money in selecting the proper instrumentation.

The article examines the virtues of the instrument interconnection technique (the IEEE-488 bus) widely available in industry which in many applications is cheaper and requires much shorter software development time than a microprocessor. The technique has great flexibility and can use hardware readily obtainable in BEIB's scientific equipment rental pool at minimal cost. Assisting investigators in evaluating different instrumentation approaches and avoiding what could be costly mistakes is one of the BEIB staff's key functions in keeping the quality of supporting services high, yet efficient.

Indeed, a review of Fiscal Year 1980 activities shows the Division is exerting leadership to develop new and more cost-effective research support for the entire biomedical community. These efforts take a number of different forms:

- Primate supply programs for both intramural and extramural research are being coordinated—at considerable cost savings—by the Interagency Primate Steering Committee. NIH is the lead agency of the committee which is administered by the Division's Veterinary Resources Branch. The committee has issued a National Primate Plan and during the past year initiated a number of projects, including one with the World Health Organization, to assure a continuing adequate supply of various species through conservation measures and captive breeding programs. A new center was created to breed and rehabilitate chimpanzees—an endangered species no longer procurable in the wild—from stock presently in the United States.
- Methods are being improved for monitoring the genetic purity of strains of research animals. The Division has issued a strain catalogue for 150 rodents to help researchers expedite the procurement of animals. Many of these strains were bred by the Division to serve specific research needs.
- The care of research animals is being advanced by development of new methods of handling, including ways to minimize behavioral problems. Standardized laboratory animal diets formulated by Division nutritionists are being widely used throughout the scientific community—also helping assure better quality animals at lower costs.
- Biomedical engineering is finding more applications in collaboration with clinical reseachers. Recent studies by BEIB in support of the National Cancer Institute include a process for whole body hyperthermia treatment of cancer patients, the relationship between chemotherapy and impairment of the wound healing process, and measures of oxygen consumption by patients under varying clinical conditions.
- The Division has created a central microanalytic facility to develop new techniques and make them available to all NIH researchers - another forward step in providing services efficiently.

As these examples suggest, the work of the Division, which is organized primarily to serve intramural NIH research programs, is having a growing impact upon NIH extramural programs as well. Over time, we expect that closer coordination of services for the two programs, such as the procurement of laboratory animals from commercial breeders, can benefit from economies of scale and centralized quality control. This, in turn, can mean greater uniformity of animals for both programs, allowing research results to be compared more realistically.

Reorganization of Safety Programs

A plan has been developed by the Director of NIH to reorganize some of the service units so that support programs for intramural and extramural research can be coordinated within new organizational structures. During the year, the first step in the plan was executed with the creation of a new Office of Research Services under the Director, NIH. This office is now responsible for administrative services, facilities engineering services, and the NIH safety programs.

Under this reorganization, the Division's Environmental Safety and Radiation Safety Branches were transferred to the new office along with other safety programs on the campus to form a new Division of Safety. The management and operations of the Division of Research Services remain as before, reporting directly to the Director of NIH.

Financial Operations

The reorganization had an affect on the Division's budget for the year. Expenditures totaled approximately $25.5 million, a decrease of $2.5 million from FY 1979. The permanent staff declined to 451 from 555 full time positions. As the accompanying Table indicates, the budget decrease was almost entirely attributable to the transfer of the environmental health and radiation safety programs out of the Division. The only other decrease was in the Veterinary Resources Branch—about $151,000. This reflects a decline in our primate quarantine activities resulting from the fact that no rhesus monkeys were available for purchase and import.

Funding for the other three branches increased. Approximately $800,000 of BEIB's increase went into additional purchases of scientific equipment for the rental pool; most of the remaining amount was expended for equipment and renovation required by the new physical microanalysis facility. The Library's automation program was increased by nearly $600,000. A greater amount of contracting for graphics, the result of higher demand by NIH investigators for these services, accounted for the $740,000 increase in spending by the Medical Arts and Photography Branch.

Outlook for FY 1981

Demand for the Division's services and products has been increasing at the rate of 20 to 30 percent a year in many areas and especially in requests filled by the Library and the Medical Arts and Photography Branches. To meet an anticipated greater demand in FY 1981, we will continue to increase our efficiency at the same staff manpower level. This will be accomplished by installing more automated systems and the employment of overtime and outside contractors.

Automation will be applied in greater degree to control the circulation of journals by the Library, to increase the output of graphics, and maintain record-keeping on animals.

Contract breeding programs of primates will be expanded to offset the continuing shortfall of wild-caught monkeys. The primate program also will concentrate on breeding additional species, long-term holding, and research and development.

We will keep expanding the amount of hardware available in the BEIB scientific equipment rental pool. This has proven to be one of the Division's most popular programs. Investigators have discovered the rental pool is a top source of equipment —and usually the most cost-effective way of obtaining what they need in the shortest time.

In sum, the Division will continue to step up the efficiency of its operations as it prepares for another productive year in delivering products and services of the highest possible quality in support of all phases of research at NIH.

Division of Research Services Annual Budget (in thousands of dollars)

	FY-79	FY-80	Increase/ Decrease
Veterinary Resources	$10,197	$10,046	$ -151
Biomedical Engineering & Instrumentation	7,039	8,462	+1,423
Library	2,137	2,731	+594
Medical Arts & Photography	3,536	4,276	+740
Environmental Health & Safety	5,162		-5,162
Total	$28,071	$25,515	$-2,556

The Division of Research Services

The many specialized functions of the Division are designed to support all of the 18 Bureaus, Institutes, and Divisions (BIDs) which constitute the National Institutes of Health. The primary program emphasis, however, is directed at serving the 5,000 staff members of the intramural program, including more than 2,400 doctoral level scientists who conduct research in NIH laboratories.

Organizationally, the Division is structured to provide products and services in support of the sequential steps in every biomedical research project: planning, making available models and substrates, manipulating and measuring research materials, and recording and communicating research results.

- The Library Branch possesses or has access to virtually all published biomedical knowledge to assist the investigator in planning and designing his/her project.
- The Veterinary Resources Branch provides the animal models, organic materials, and proper facilities for their use.
- The Biomedical Engineering and Instrumentation Branch collaborates with the investigator in devising the means whereby research materials may be manipulated and results measured, often with highly sophisticated electronic equipment.
- Finally, the skills of the Medical Arts and Photography Branch are available to all investigators to enable them to record and communicate the results of their research to the scientific community.

Biomedical Engineering and Instrumentation Branch

Murray Eden, Ph.D., Chief

During Fiscal Year 1980, the Biomedical Engineering and Instrumentation Branch continued to provide a wide variety of specialized engineering and physical science skills to the NIH research community. BEIB engineers collaborated in more than 200 projects to produce advanced instrumentation models, methods, and techniques dedicated to the acquisition of biomedical information previously not available to the research scientist.

The Branch's skills cover a great many disciplines. The staff includes 35 professional physical scientists and engineers as well as 75 technical support personnel: machinists, glassblowers, instrument makers, electronic and mechanical technicians. During the year, the Branch responded to over 3,500 requests from NIH scientists for the fabrication and modification of laboratory devices and made another 8,000 repairs or minor changes to scientific equipment.

The range of projects spans NIH research interests. Most entail design or refinement of instruments to measure, observe, or describe in *vitro* or in *vivo* biological systems in an analytic or quantitative way. The systems we have helped to study represent virtually every level of organization; biomedical, cellular, organ or tissue, and holistic.

In the fall of 1979, BEIB sponsored an NIH Consensus Development Conference on "The Use of Microprocessor-Based, 'Intelligent' Machines in Patient Care." The "microcomputers" can even be implanted biologically and are creating new medical technologies—including some that may ultimately allow machines to exercise a degree of autonomy over patient care. Their application raises both technological and sociological questions:

> Would these devices truly be more reliable or cost-effective than manual methods? Would they lead to improved patient outcomes?
>
> What ethical-legal issues can arise in their development, testing, and marketing?
>
> What might be their long-term, adverse consequences? How could these ill-effects be avoided?
>
> How might one verify that the devices perform those functions—and only those—which their designers intended?

The conference was organized to allow practitioners, researchers, and others to discuss these issues during a formative stage of the technology's development, so as to guide it along lines that would be responsive to society's needs. A series of working papers (NIH Pub. No. 79-1852) prepared for the conference may be obtained from BEIB. A book containing a number of the papers presented at the conference, as well as the working papers, is to be published in Fall 1980.

BEIB's professional staff functions under four sections and a program (in physical microanalysis) currently contained within the Office of the Chief. Here is a brief review of FY 1980 activities:

Applied Clinical Engineering Section—This multi-disciplinary group, physically located within the NIH Clinical Center, works directly with biomedical scientists in patient settings. During the year, a whole body hyperthermia project was completed. The system is intended to reduce the population of growing cancer cells by maintaining patients with cancer at elevated temperatures on the theory that dividing cancer cells are more sensitive to higher temperatures than normal tissue cells. At these elevated temperatures the physiological system of man loses its ability to regulate body temperature. The engineering system must hold the heat supply fast at the edge of the temperature zone living tissues can tolerate. The treatment, employed over 500 times, has proved to be able to raise the whole body core temperature in humans to 41.8°C and to maintain that temperature within one-tenth of a degree for periods as long as four hours.

Studies were completed on the strength of newly grown repair tissue, an issue that bears on the treatment of cancer. Cancer specialists have suspected that the chemotherapy provided to patients after they have undergone surgery for tumor removal has acted upon the growing cells of the repair tissue and impaired the wound healing process. Wound breaking strength measurements made on the surgically wounded skin of rats showed that the agent adriamycin causes the repair tissue to be significantly weaker, but that impairment of healing can be minimized by suspending the administration of the therapeutic agent for three or more days following surgery.

The section is currently investigating the measurement of oxygen consumption for three different clinical purposes. The Clinical Care unit requires a technique for measuring oxygen consumption in the oxygen enriched air of a ventilator. The Anesthesia Department has requested an oxygen consumption monitor for surgical procedures and workers in the National Cancer Institute have requested a system suitable for studying patients during chemotherapy. Each system has its own special constraints and will require a different technical solution.

Chemical Engineering Section—Recent work by the staff has increased the understanding of fluid flow relevant to arterial disease, and of the movement of chemicals in the body. Other developments include new instrumentation involving synthetic membranes and innovative application of synthetic polymers to very small catheters.

The appearance of atherosclerotic lesions (fatty deposits) at specific locations in the arterial tree has led many investigators to conclude that forces exerted by the blood may be a factor in the initiation and progression of the disease. The natural arterial network is extremely complex, however, and direct observations of blood flow in animals and man are difficult or impossible. Therefore, the section has constructed simplified plastic and glass models which permit many important measurements to be made. These measurements include wall shear stress and mass transfer by an electrochemical technique, velocity profiles by laser anemometry, and direct visualization of flow patterns by use of dye injection or tracer particles. They are expected to correlate with the incidence and location of the disease. It is already clear that rather subtle changes in geometry can have a profound effect on the flow patterns.

Principles of chemical reaction engineering have been applied to the problem of predicting the concentration-time course of foreign chemicals in the body. This has considerably improved the section's ability to generalize from one animal species to another and to design potentially improved and more rational drug therapies from fundamental principles. The section has examined the distribution of polychlorinated biphenyls in the tissues of several mammalian animal species and have developed a mathematical model to determine what aspects of the distribution can safely be predicted from one species to another, what aspects must be measured, and how these measurements could be used to predict the tissue burdens in humans exposed to environmental contaminants. Similar concepts were used to design anticancer drug protocols for the treatment of ovarian cancer or other malignancies confined to the peritoneal region.

Synthetic membrane technology is having a significant impact on the ability to design laboratory and clinical instruments which depend for their function on separation of two regions such as blood and a chemical sensor but which allow safe transfer of certain components essential to the measurement or process being conducted. For example, in collaboration with the Mechanical Engineering Section, one member of the section's staff developed a miniature probe to measure the acid concentration (or pH) of blood by a purely optical technique using a polymer-bound dye indicator. Patents on the pH probe are currently under discussion for licensing by the Government to private industry.

Electrical and Electronic Engineering Section—The section's principal initiative was devoted to developing a capability to implement "smart" instrument systems based on a new industry-wide standard interconnection system (see page 9). The section acquired a programmable calculator for use as a controller in such systems, and gained experience on several relatively simple applications. The section's resources for developing microprocessor-based instruments also were upgraded.

Much effort was applied to several major projects which are approaching completion, including a high resolution positron emission tomograph, an imaging system based on nuclear magnetic resonance, and a microprocessor-based instrument for use in the patient electrical safety program. Other microprocessor-oriented projects were completed for use in the areas of mass spectrometry and temperature measurement.

Mechanical Engineering Section—Most of the staff's efforts were spent on such long-term projects as a family of miniature catheters, a family of indwelling fiber optic miniaturized physiological sensors, microcalorimetric probes, radically improved techniques for neural mapping, and noninvasive blood pressure measurement. Mechanical design was performed for several large interdisciplinary projects, e.g., the NMP Imaging Magnet and the PET Scanner.

One of the novel types of miniature catheter advances through narrow tortuous blood vessels by turning itself inside out. The catheter is constructed by passing a miniature plastic tube (0.075 mm wall x 1 mm diameter) through a conventional catheter and bonding the two together at the distal end. After the conventional catheter is advanced into the vascular system as far as possible, the annular space between the two tubes is pressurized, forcing the inner miniature tube to move out of the outer tube, everting as it advances. The mode of operation avoids the buildup of friction forces between the blood vessel and the catheter which limits the travel of conventional and balloon catheters. It allows placement in the venous system, and eliminates vascular irritation arising from relative motion between the catheter and the wall. It is anticipated that the catheter will be used for highly localized selective delivery of fluids which will provide chemotherapy or solidify to block blood flow through vascular lesions.

Physical Microanalysis Group—The 200 keV microscope was moved to its permanent location, a 50 keV scanning electron microprobe was installed, and interfacing of a large laboratory computer to the electron microscope was begun. The computer will be used in an on-line mode connected to both the microscope and microprobe, permitting high speed transfer of images and spectra. This will allow the investigator to effect data reduction and manipulation of both spectra and images and then utilize the results to determine the next step of the analysis.

Scientific Equipment Services

During FY 80, the Technical Services of BEIB was reorganized into five sections and the name was changed to Scientific Equipment Services. SES responded to about 11,500 work requests at a cost of over $3,000,000 during the year. The new sections and their functions are as follows:

Mechanical Design and Scheduling Section—This section designs mechanical instruments and equipment to be fabricated for investigators inhouse and on contract. Contracted work is checked by BEIB technicians to assure that it meets design specifications before it is forwarded to the researcher. Approximately 550 instruments and devices valued at $230,000 were fabricated on contract this year.

Mechanical Instrument and Fabrication Section—This section makes mechanical instruments and also develops improved fabrication techniques. The section is composed of the following: Glassblowing Unit, Precision Instrument Unit, and the Machine and Welding Unit.

Clinical Care Instrumentation Section—Located in the Clinical Center, this section provides maintenance, repair, testing, evaluation, modification, design, safety checking and fabrication of clinical care equipment. To increase efficiency of semiannual preventative maintenance and safety checks of clinical care equipment, the section is switching from a manual to an automated system.

Research Instrumentation Section—This section provides maintenance, repair, testing, evaluation and modification of research equipment and the design and fabrication of electronic and electromechanical equipment. The section consists of a mechanical unit and two electronic units.

Materiel and Clerical Operations Section—This section maintains an inventory of commodities to support the operations of Scientific Equipment Services. It provides secretarial assistance, job processing, and recordkeeping systems.

Scientific Equipment Rental Program—This program is continuing to expand at a rapid rate to meet the needs of the NIH scientific community. Five hundred instruments valued at $1.5 million were added to the rental pool program this year. The program features same day delivery of available items. If a needed instrument is not in the inventory, the purchase of one that meets the investigator's specifications will be arranged.

Two Competing Approaches in Developing Custom Instrumentation

By Walter S. Friauf
Chief, Electrical and Electronic Engineering Section, BEIB

Rapid advances in the complexity and sophistication of scientific research have created severe problems for those called on to provide engineering and instrumentation support. It is true that advances in electronic technology also have been extremely rapid and far reaching, but bringing these advances to bear quickly and effectively is not easy. In fact, the task of simply evaluating the relative merits of all the instrumentation approaches that might be applied to a given experiment calls for encyclopedic expertise.

The technological resources of NIH are limited. A wrong choice can be costly not only in money, but also in the time and services of the technical professionals. For these reasons, it is useful to make a closer examination of the two major competitive developments in electronics of the 1970's.

The Microprocessor — High Software Costs

The first is the microprocessor. These are large-scale integrated circuits which serve as the central processing units of microcomputers. As such, they are key components, controlling the interpretations and execution of machine instructions. The system's perceived importance to intramural research is such that at least five different sections at NIH are applying this device. Nonetheless, its use in research has had a much different impact than in the electronics industry because of differing circumstances. Industry designs powerful instruments which are then mass-produced, allowing the R&D costs to be prorated. Each mass-produced instrument is relatively cheap because the hardware complexity is reduced by use of the microprocessor and software can be replicated at virtually no cost.

Unfortunately, neither of these latter benefits can be realized at NIH where most custom instruments are one-of-a-kind developments. Consequently, the high software development costs in programming time offset, at least in part, the other advantages of the microprocessor. Moreover, at NIH specifications for the appropriate instrumentation usually must undergo a considerable evolution as the research progresses. In industry when a marketable product has been developed there may be little further need for additional software. While it might be thought that the flexibility through software of the microprocessor would be ideally suited to deal with changing needs, in reality the preparation of software for microprocessors is a slow process. Furthermore, major changes in the specifications in the course of the experiment can affect hardware inputs and outputs as well.

Flexibility of the "Bus" Approach

A second major electronic development of the 1970s, derived from the engineering community's concern for compatability of equipment, is the instrument interconnection technique - the IEEE 488 interface bus standard. The IEEE bus standard allows "smart" instrument systems to be developed by interfacing a controller and a group of standard commercial instruments and devices. For example, a system could include solenoid valves, stepping motors, and heaters to control an experiment; a pulse generator to provide stimuli; voltmeters, counters, and an electronic thermometer to make measurements; and a printer and X-Y plotter to present data and results.

All of these devices can function under program control provided by software for a programmable calculator or other controller, which would also provide data processing capability for the system. The controller would contain a microprocessor which provides control and computational power, but in this configuration neither the designer nor end user of the system would deal directly with the microprocessor.

Hardware development costs for such systems are virtually nil because all the components are interconnected by simply plugging in standard cables. Changes during development can be accomplished merely by unplugging and plugging in other instruments or more of them.

Of course, software is needed but the Biomedical Engineering and Instrumentation Branch's (BEIB) experience indicates that it can be developed much faster for a programmable calculator than for a microprocessor-based instrument. The reasons for this are not immediately obvious, but there seems to be a combination of several important factors. First, the bus interconnected system is inherently modular. This simplifies system checkout and eliminates a great deal of time spent determining whether the problems are with the hardware or the software. Second, much of the software needed for interfacing instruments is made available by the manufacturer with the instrument. Finally, the calculators usually used as controllers have been developed to satisfy a market of users who want to be able to write software simply. Accordingly, the manufacturers provide programming facilities which make software writing as accessible as possible. This has the additional benefit of making it easier for the user to modify and extend the software after the system has been delivered.

Saving Development Time

We have been in a position to compare the software development times for the two approaches on a number of systems of comparable complexity, and in one case, systems providing essentially identical functional capability. In all instances the lower development time for the bus system is very pronounced - usually approaching an order of magnitude. This is the factor of greatest significance at NIH.

Naturally, there are some disadvantages. The hardware component cost is much higher and the systems are larger. The first problem may be alleviated by utilizing components leased from the BEIB scientific equipment rental pool as much as possible. This also can greatly reduce delivery time delays. The same components can be reused over and over as instrumentation needs change.

If the size of the system becomes a problem it can subsequently be reduced to a custom microprocessor-based instrument. This approach may be easier than starting out with the microprocessor -especially when considerable experimentation is needed first to obtain the desired instrument specifications. We have just completed such a developmental sequence with excellent results. The most gratifying aspect was the simplification of software development for the microprocessor-based instrument even though the software developed for the bus system was not directly transferrable.

The bus approach will continue to evolve as more and more instruments - electronic balances, microscope stage drives, and the like - become available with the standard interface. New types of controllers also will appear. While the desk top calculators normally used as controllers so far have been very satisfactory, they were not developed primarily for that purpose. One radically different controller has appeared on the market so far, and the possibilities in this direction are unlimited. We can also look forward to a great increase in standardized modular software for such systems.

Thus the interface bus standard, though virtually unheard of in comparison to the microprocessor, may well be the electronic development of the '70s that is of primary significance in the '80s at facilities such as NIH with urgent, specialized, and constantly changing instrumentation requirements. We are building up our resources to exploit this technology.

Library Branch

Ruth C. Smith, Chief

This fiscal year saw the trend toward maximizing the accessibility of information enhanced and an increase in the effort to minimize the time loss by patrons in the use of the Library resources.

- The Library plans to upgrade its limited computer facilities. Authorization was received to purchase a turn-key mini computer system in order to automate the entire Library. Assisted by the staff of the Systems Design Section, Computer Systems Laboratory, DCRT, a request for proposal was prepared. It is now in the hands of the Negotiated Contracts Unit, Contracts Operations Section, Procurement Branch.
- To increase service to patrons the Reference and Bibliographic Services Section has made the following changes: (1) two reference staff members are now assigned to the upper level reference area; (2) telephones have been installed on the reference desks to take advantage of the proximity of the reference tools; and (3) the lower level reference desk has been replaced by a "help" telephone connected to the upper level desks.
- The Stacks and Copy Service monitors a self-service photocopying activity which totals about 1.5 million pages annually. To handle this enormous and ever-increasing volume and shorten the time it takes an individual to photocopy an article, one of the three copying machines was designated "express" for 15 pages or less and the other two machines were set aside for copying up to 30 pages. The 24-hour service was terminated.
- Processing of periodicals currently is controlled by the PHILSOM (Periodicals Held In Libraries of Schools of Medicine) automated serial records system operated by the Washington University School of Medicine, St. Louis. This is being converted from a batch system to an on-line system to increase its efficiency.
- The Translation Unit has added a translator and is working to improve its "flash" service to notify NIH investigators of newly available translations. During the year, the Unit completed the first translation into English of a part of the original 1882 monograph "Ueber die Multiplen Fibrome der Haut und Ihre Beziehung zu den Multiplen Neurome" by Frederick von Recklinghausen. This will comprise a chapter in a symposium on von Recklinghausen's disease being edited by Dr. John J. Mulvihill of the National Cancer Institute. The symposium will be published by Raven Press in the Fall of 1980.
- The Library also has centralized its purchasing and procurement for all units within the Administrative Office. This has speeded up the acquisition of materials needed to provide prompt service.

Outlook for FY 1981

Several of the modules for the new automated system are expected to be installed in the coming year. They will be those presently operational, such as circulation control and on-line catalogs. The Library will accept others, such as acquisitions and journals control, as they become available.

Lack of space in the journals collection continues to be a problem. Hard copies are being replaced with microfilm copies. As original volumes are removed, the microfilm cassettes will be located on the shelves in the correct alphabetical order, rather than in separate file cabinets. This will save library users from having to search for journals in more than one location.

HAIR
BLOOD VESSELS
HAIR FOLLICLE
SWEAT GLAND

Medical Arts and Photography Branch

Arthur F. Moore, Chief

Continuing the trend of prior years, demand for photographic, graphic arts, and other services increased by 26 percent in Fiscal Year 1980 - reflecting the expanding amount of new biomedical knowledge being generated by NIH investigators. Most of the Branch's work assists scientists in recording the results of their research and communicating it in published articles and papers.

The Branch's staff of 52 artists, photographers, and other specialists are highly skilled in meeting the needs of scientists for graphic presentations, still and motion picture photography, including photomacrography and photomicrography, and medical arts. Services also include the design and production of publications; the preparation of slides, vugraphs, and other projected visual aids; animation artwork; technical, general, and medical illustrations; exhibit design; statistical drafting; display charts; posters and medical models.

The philosophy of the Branch is to provide high quality professional services competitive in cost with commercially obtainable services. The staff monitors all graphic and photographic services procured by outside contract to assure quality standards are kept.

The heavier demand for finished artwork during the year was met by a corresponding increase in contract services and an acceleration in deliveries. Photographic services and graphic services are performed normally in five workdays. But 24-hour emergency service is available. Design work is turned out in 10 workdays; this time also may be reduced by the Branch staff in special cases.

Adequate leadtimes are the key to producing quality audiovisual materials at reasonable costs. Experience shows that many members of the NIH community fail to allow enough time for planning and production; errors often crop up in submitted raw data causing delays and higher costs. The Branch has extensive expertise in conversion of data into effective multimedia presentations. This counsel is readily available for all of the Branch's services and should be used earlier and with more frequency.

A graphic design manual prepared by the Branch is available to investigators to assist them in planning and producing desired visual communications. This publication is gaining wider acceptance and is helping to effect savings by establishing standards and reducing preliminary design problems. Following is a summary of FY 1980 activities:

Photography Section—Technological improvements were instituted in the areas of photomicrography, photomacrography, and photographic laboratory services. They were accomplished by increased technical training of personnel and by replacing old equipment with advanced photographic tools. The section employed outside vendor services from private photo firms in the Washington, D.C. area in addition to in-house facilities, in order to keep pace with the ever increasing calls for photography services.

Design Graphic Section—This unit is composed of highly trained, extremely dedicated personnel. The group is capable of filling requests for complex visual productions, which are continually mounting in numbers. The section had a productive year, augmenting output 20 percent with no increase in personnel and maintaining its usual high quality production. Requests for medical illustrations remained at a normal level throughout the year. Contracting was seldom used since few projects entailed short deadlines. Calls for medical models remained about the same as in FY 1979.

Motion Picture Section—The number of filming requests were about the same as 1979 with several more formal productions completed than in the previous year.

Outlook for FY 1981

Early in the new fiscal year, the graphics unit will acquire its own in-shop computer graphics capability; there will be a compatible contract backup. The photo section will install new equipment to widen the spectrum of magnification in fluorescent microscopy.

The Medical Arts and Photography Branch will continue to develop and implement a system to upgrade NIH visual communications. It will aim to improve, enlarge, and extend its services and seek additional ways to acquaint the NIH community with its skills. The importance of early counsel and planning for optimum service will be emphasized.

Veterinary Resources Branch

Robert A. Whitney, Jr., D.V.M., Chief

The program to assure future supplies of primates to meet human health needs was expanded during the year by the Interagency Primate Steering Committee, which is administered by the Veterinary Resources Branch. New projects included:

- A contract with the World Health Organization to start up an internationally-financed program to assist Asian and African nations in conserving and breeding native primate species.
- A wildlife management training program in cooperation with the Department of the Interior that is designed to improve the conservation of primates in Central and South America. The program is being operated by the University of Florida. A second conservation and breeding program for New World primates was launched with the Pan American Health Organization.
- Creation of a center for rehabilitating and breeding chimpanzees from among the present U.S. population of approximately 1,300 chimps held in zoos and by research laboratories. The center is being operated by the University of Texas. Chimpanzees are an endangered species that no longer can be taken in the wild.

The committee has issued a National Primate Plan to coordinate all conservation and breeding programs in the U.S. in order to offset the shortage of rhesus monkeys and other species needed for scientific purposes. About 35,000 primates are used annually by the U.S. biomedical community, mainly in Government-supported programs.

NIH, the principal agency funding biomedical research, is the lead agency on the committee. The membership of the committee is composed of representatives from the National Science Foundation; the Department of Defense; the Alcohol, Drug Abuse and Mental Health Administration; the Center for Disease Control; the Food and Drug Administration; the Office of International Health; the Veterans Administration; the Environmental Protection Agency; the State Department; the NIH Division of Research Resources; and the Office of Program Planning and Evaluation, NIH.

Comparative Reproductive Laboratory—In another major development, the VRB established a Comparative Reproductive Laboratory during the year that will develop a cryopreservation program for the storage of genetic material—embryos and spermatozoa—of unique animal models used in NIH research. This is to ensure that such valuable species as inbred rodents that comprise the international genetic resource will be available for future research programs.

The laboratory is conducting collaborative research with units of NIH and other Government agencies. The work centers on defining reproductive relationships and requirements of laboratory, domestic, and endangered species with particular emphasis on the development of animal research models for the study of human disease. These latter species include the VRB Animal Center's foxhound colony, monkeys, cats, goats, and inbred miniature pigs in addition to rodents. Laboratory personnel also furnish information and technical assistance to the biomedical community on fertility evaluation—employing such techniques as semen collection and evaluation, laproscopy, radioimmunoassays, and statistical analysis.

Staff Animal Behaviorist—In a further step to enhance the quality of animals supplied by VRB, a staff animal behaviorist was employed to identify environmental needs unique to each species. Enrichment programs are being developed to better match the environment to the animals' needs. Together with improved genetic definition and nutrition, this will reduce variabilities caused by stress, enabling the use of fewer animals.

VRB's programs are conducted through four sections. Here is a brief review of their FY 1980 activities:

Animal Center Section—This section produces, maintains, and develops large laboratory animals and provides related services and products for NIH investigators. The animals involved are mainly primates, farm animals, and carnivores (dogs and cats). Purebred foxhounds, swine, and monkeys are provided by breeding colonies.

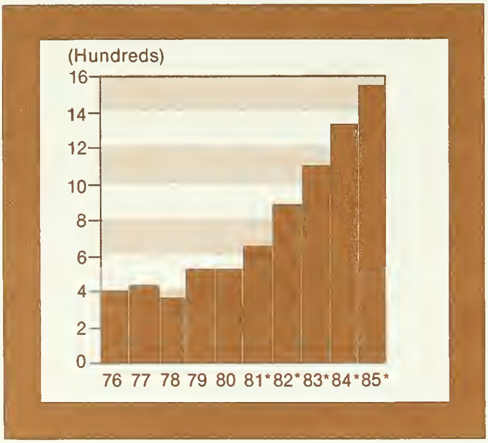
The Primate Quarantine Unit is procuring wild-caught cynomolgus monkeys for polio vaccine testing and NIH intramural research in place of rhesus monkeys. The rhesus supply has not been re-established since the last animals were received from Bangladesh in January 1979. Cynomolgus monkeys are arriving sporadically from Phillippine and Indonesian sources. All male rhesus monkeys from the VRB contract production colonies are being utilized for polio vaccine testing. This is expected to continue until 1982. All female rhesus monkeys produced are being held as replacement breeders for domestic colonies.

The two VRB contract production colonies of monkeys are being expanded to supply intramural and other Government agencies. The expansion is in accord with National Primate Plan objectives and will involve mostly cynomolgus monkeys and certain New World species. Current production levels are within expectations (see Figure 1).

The National Cancer Institute's herd of inbred miniature swine will continue to be maintained by the Ungulate Unit at approximately 200 head in order to provide sufficient progeny for histocompatibility and transplantation studies. During the past year, surplus NCI animals were sent to several laboratories to be used as breeding stock.

Automated plasmapheresis is being used to collect blood from livestock. The plasma can then be clotted to yield serum. This procedure provides an efficient method of collecting large volumes of plasma from a single animal. It also can selectively collect different blood components. Since its inception the demand for this service has continued to increase. The total number of livestock held has increased significantly over the past several years along with the number of livestock bleeding procedures.

Figure 1
Rhesus and Cynomolgus Monkey Production



*projected

The foxhound breeding colony is in the process of being moved to new facilities and increased puppy production is expected. For the third straight year, over 1,000 foxhound puppies were born. About 950 dogs were issued this year. The number of cats procured, quarantined, and issued per year is approaching 900 and is expected to remain at that level.

Comparative Pathology Section—This section is responsible for the health status of the laboratory animals produced, quarantined, or utilized in biomedical research at NIH. It also assures the genetic quality of NIH animals, which are shipped worldwide as a function of the World Health Organization-sponsored Genetic Resource.

The number of autopsies performed by the pathology service this fiscal year is 4,575, an approximately 110 percent increase from last year. This increase was caused by an outbreak of mousepox that was first diagnosed on November 28, 1979. The outbreak involved three NCI animal rooms on the fourth floor of Building 10 as well as a number of rooms in NCI-contracted holding space off campus. Also, a large amount of work was generated by the occurrence of false positive serologic tests for mousepox in another NCI contracted holding space. As a result of the outbreak, the number of samples processed for endo and ectoparasite monitoring, contracted virus monitoring, and hematology was 22,703 - a 327 percent increase over last year (see Figure 2).

Small Animal Section—Approximately 324,600 rodents and rabbits produced within VRB were issued for intramural research - a slight decrease from last year. This represents a continuing trend resulting from contracting production activities.

There was a slight decline in utilization of VRB-produced mice and rats. On the other hand, total issues of guinea pigs, hamsters, and contractor-produced rabbits increased slightly. Total purchases of rodents and rabbits from contractors rose from 648,000 to 683,000 (Figure 3).

There was no evidence of any compromise of genetic quality in any of the breeding goups during the year. Requests for new introductions are increasing; currently, there is a backlog of approximately 50 stocks and strains. New introductions during the year included the nude rat (*rnu*), and the RCS/N-*rdy-c*, RCS/N-*rdy-p*, and the RCS/N-+-*p* congenic rat strains. One inbred mouse strain (C3H/HeJ) and two mutant strains (dwarf and viable yellow) were introduced. One rat strain (RLA/N) was lost due to reproductive failure.

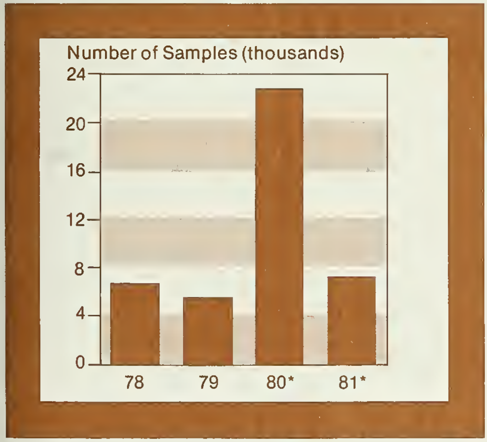
The introduction of the nude mouse gene into a number of inbred backgrounds is nearly complete. The demand for various nude mice, including the double deficient T and B cell mouse (NIH II-nu), continues to exceed available supply. This model has proven to be valuable in cancer, parasitic, and infectious disease studies. Development of an outbred rat (N:NIH) for use in general population studies such as alcohol abuse, etc., is nearly complete.

The nutrition program has been occupied with the concerns of the biomedical research community regarding the potential for chemical contaminants in laboratory animal diets. A limited amount of data procured to date indicates contaminant concentrations in NIH feed are typically below concentrations shown to adversely affect diet quality. Approximately 50 nitrosamine assays have been completed on samples of various NIH animal feeds. A new rodent diet manufactured without ingredients of animal origin to minimize contaminant concentrations is being evaluated.

Requests for assistance on problems related to animal nutrition were received from Peru, Columbia, Argentina, Mexico, the United Kingdom, Germany, and the Phillippines. The Section assisted development of adequate diets for recently established primate breeding colonies in South America. The Environmental Protection Agency and the National Toxicology Program also requested aid in establishing nutritional test standards. Investigators at NIH appear to be quite sensitive to the effects nutrition may have on experimental results. Hence, numerous requests are made for nutritional information or modifications in diet formulations to accommodate specific program requirements.

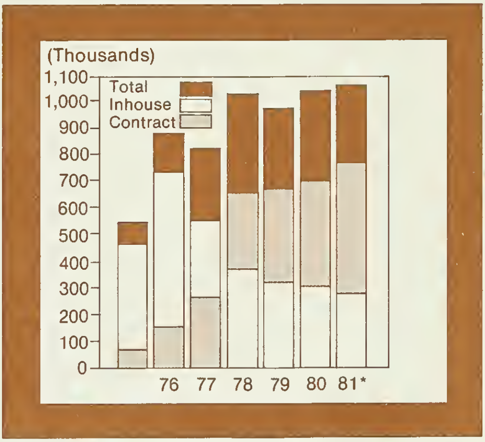
Veterinary Medicine and Surgery Section—Renovations in the central animal surgical area neared completion and the facility has been well equipped. This facility could be added to the list of potential auxiliary infirmaries in the event of a national disaster where emergency medical services are needed.

Figure 2
Clinical Pathology Samples



*projected

Figure 3
Total Animals Issued



*projected

The minipig continues to grow in popularity as the animal model of choice for many investigations. Studies with cat leukemia necessitated housing cats in isolators. There is a trend toward increased use of small ruminants such as sheep and goats (Figure 4).

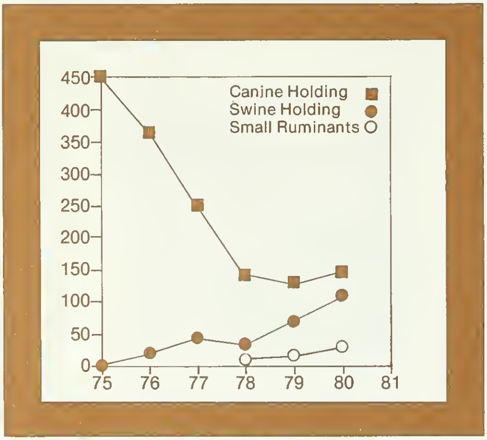
The nonhuman primate holding facility reached its capacity of 1,200 animals. Additional space was acquired through interagency agreements with the Department of Defense and the use of the Primate Quarantine Unit, NIH Animal Center, on a temporary basis. The primate recycle program continues to be viable. Issues were at an all-time high due, primarily, to unavailability of imported rhesus monkeys. Breeding of timed pregnant primates conducted in-house and on contract provided approximately 150 neonates. Needs were less than projected due to the shift in NIH intramural research emphasis.

Outlook for FY 1981

The Comparative Reproduction Laboratory program will be expanded. Artificial insemination techniques using both fresh and frozen spermatozoa will be tested in the foxhound breeding colony. The radioimmunoassay program, currently designed to analyze serum for steroid hormones, will be extended to protein hormones - including luteinizing hormone, growth hormone, and prolactin.

Figure 4

Comparative Medicine Unit Average Monthly Holding



The Animal Center will add facilities to accommodate more livestock and dogs. Additional dog pastures also are to be constructed. A data processing system is being developed for the Carnivore Unit. It will be expanded and incorporated into other Animal Center activities.

Future primate supply activities for NIH and other agencies will rely upon expansion of contract breeding operations. The program will become more involved with breeding exotic species of primates, long-term holding, research, and development.

The first phase of a data processing program for the Small Animal Section is scheduled to be implemented during the next fiscal year. Development of the computer program and purchase of the initial hardware is planned for the fourth quarter of FY 1980. The Strain 2 and Strain 13 guinea pig production colonies will be contracted to commercial breeders.

BIOMEDICAL ENGINEERING AND INSTRUMENTATION BRANCH

DIVISION OF RESEARCH SERVICES

NATIONAL INSTITUTES OF HEALTH

ANNUAL REPORT FY 1980

Dr. Murray Eden, Chief

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 RS 10001-12 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Pharmacokinetics

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.L. Dedrick	Chief	ChES BEIB DRS
	J.M. Collins	Chemical Engineer	BEIB DRS
OTHER:	D.S. Zaharko	Pharmacologist	LCHPH NCI
	F. King	Associate Professor	Howard Univ.
	A.M. Guarino	Chief	LT NCI
	R.J. Lutz	Chemical Engineer	BEIB DRS
	M.W. Anderson	Mathematician	PB NIEHS
	P.M. Bungay	Chemical Engineer	BEIB DRS
	H.B. Matthews	Pharmacologist	NTP NIEHS
	I.G. Sipes	Assistant Professor	Univ. of Arizona
	C.E. Myers	Oncologist	CPB NCI
	J.L. Speyer	Oncologist	MB NCI
	M.F. Flessner	Chemical Engineer	US Coast Guard

COOPERATING UNITS (if any)

LCHPH-NCI; PB-NIEHS; AK-CU Program NIAMDD; M-NCI; NTP-NIEHS; CPB-NCI.

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
4.0	3.0	1.0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Pharmacokinetic models are developed for the distribution and disposition of drugs, environmental contaminants, and endogenous metabolites in animals and man. They provide a plausible set of equations that can be used to extrapolate data from animals to man and thereby improve chemotherapy, hemodialysis, and risk assessment.

PHS-6040
(Rev. 10-76)

Objectives: Improve and extend mathematical models for the distribution and disposition of drugs, environmental contaminants, and endogenous metabolites in animals and man to:

(1) Account for species differences in drug distribution.

(2) Provide a rational basis for extrapolating toxicity from animals to man.

(3) In conjunction with pharmacodynamics, provide a basis for optimizing cancer chemotherapy and chronic hemodialysis.

(4) Enable rational transfer of *in vitro* thermodynamic and kinetic data to *in vivo* cases.

(5) Predict effective dose schedules of anticancer drugs in individual patients with particular emphasis on intraperitoneal drug administration.

Methods Employed: Mathematical models are developed from physicochemical, physiological, and anatomical information and the principles of chemical reaction engineering. Resulting sets of differential equations are solved analytically or numerically and compared with experimental data. Uncertainties are clarified by additional experiments and model modification.

Major Findings:

(1) A pharmacokinetic model developed to describe the distribution and disposition of polychlorinated biphenyls in the rat has been employed to analyze data from the dog and monkey. Estimates of tissue blood flow were used as intercompartment transport parameters for all tissues except skin; as had been observed in the rat, skin of the monkey and dog appeared to exhibit significant departure from flow limitation. Partition coefficients between several major tissues and blood are similar for 2,4,5,2 ,4 ,5-hexachlorobiphenyl in rat, dog, and monkey. The intrinsic rates of metabolism of this compound and of the 4,4 congener (ml/min kg body weight) are highest in the dog and lowest in the monkey. The importance of position of the substituents is shown by the fact that the intrinsic rates of metabolism of 2,3,6,2 ,3 ,6-hexachlorobiphenyl are more than an order of magnitude higher than those of the 2,4,5-isomer in both dog and monkey. Kidney clearances of lumped "metabolite" (per unit of body weight) are low, with the rat exhibiting somewhat higher values than the dog or monkey for the two congeners for which data exist in all species.

(2) An analysis was performed of the disposition of chlordecone (Kepone) in the rat. Particular attention was devoted to the role of the intestinal tract in excretion, as well as absorption, of this halogenated pesticide. The chlordecone disposition was quantitated by development of a mathematical model of the physiological pharmacokinetic type. The model includes a detailed description for the GI tract in which the organs of the GI tract are segmented into a series of well-mixed compartments representing stomach, small intestine, cecum, and large intestine. The model is applied to describing the movement of a nonabsorbable tracer along the GI tract in addition to the enteric transport of chlordecone. Values for the gut wall permeability-area products for chlordecone were determined for the rat and estimated for man based on scale-up considerations. The potential for enhancement of excretion rates from victims of poisoning by lipophilic chemicals through use of orally administered adsorbents was examined.

(3) A two-compartment physiologically-based pharmacokinetic model has been developed to describe the clinical pharmacokinetics of the anticancer drug 5-fluorouracil (5FU) following intravenous administration of a rapid bolus or continuous infusion. The principal feature of this model is its ability to explain the differences in clearance observed between these two schedules by the use of saturable whole body clearance. The model has also been extended to simulate intraperitoneal administration.

(4) Our understanding of intraperitoneal drug kinetics has been enhanced by a clinical study in which catheters were placed in the portal vein, hepatic vein, an artery and a peripheral vein. Samples were obtained from these sites and also from the peritoneal fluid during 5FU administration. Calculations of hepatic extraction and estimates of the fraction of drug absorbed via the portal system were made from this unique data set.

(5) The initial results obtained from adriamycin administration in the large volume intraperitoneal protocol have been in agreement with predictions - made from scale-up of rat experiments and modifications of systemic pharmacokinetic models. Distributed models of peritoneal uptake are currently being explored.

(6) A physiologic pharmacokinetic model is being developed for 2'-deoxycoformycin (DCF) in the mouse. The major route of excretion of DCF is through the kidneys. Kidney clearance of DCF is nearly twice the estimated glomerular filtration rate indicating considerable tubular secretion. No metabolites of DCF have been found in the urine, but a small amount of a phosphorylated species forms intracellularly. DCF is a tightly bound inhibitor of the ubiquitous enzyme adenosine deaminase. The modeling process uses a sequential parameter estimation procedure. The parameters for the individual tissues are fitted using a hybrid model consisting of model equations for the specific tissue and a curve-fitted equation for the plasma data. The pharmacokinetics for the total animal are then determined by solving all equations simultaneously and predicting the plasma concentration from the mass balance.

Significance: Drugs and other chemicals are tested for effect in animals, with the aim of extrapolating results to man. At issue are both the risk associated with environmental contaminants and optimization of therapy.

Proposed Course: Continued pharmacokinetic modeling with consideration of pharmacodynamic and cytokinetic events and drug interactions. Continued clinical emphasis through support of intraperitoneal procedures and other measures to overcome drug resistance. Increased emphasis on research designed to investigate distribution and metabolism of environmental contaminants. Investigation of use of *in vitro* assays of chemical metabolism in conjunction with pharmacokinetic models for quantitative prediction of metabolism *in vivo*.

Publications:

Speyer, J.L., Collins, J.M., Dedrick, R.L., Brennan, M.F., Londer, H., DeVita, Jr., V.T., and Myers, C.E. Phase I and pharmacological studies of intraperitoneal (I.P.) 5-Fluorouracil (5-FU). Proc. 15th Ann. Mtg. Am. Soc. Clin. Oncology (Abstract) 20: 352, 1979.

Dedrick, R.L. Pharmacokinetics of Vinylidine Chloride (Letter). Environmental Health Perspectives 28: 311-313, 1979.

Bungay, P.M., Dedrick, R.L., and Matthews, H.B. Pharmacokinetics of Halogenated Hydrocarbons. Ann. N.Y. Acad. Sci. 320: 257-270, 1979.

Bungay, P.M., Dedrick, R.L., and Matthews, H.B. Pharmacokinetics of environmental contaminants in Dynamics, Exposure and Hazard Assessment of Toxic Chemicals in the Environment. R. Haque (Ed.), Ann Arbor Science Publishers, 1980, pp. 369-377.

Yang, K.H., Fung, W.P., Lutz, R.J., Dedrick, R.L., and Zaharko, D.S. In Vivo Transport of Methotrexate in Murine Lewis Lung Tumor. J. Pharm. Sci. 68: 941-945, 1979.

Dedrick, R.L., and Bischoff, K.B. Species similarities in pharmacokinetics. Fed. Proc. 39: 54-59, 1980.

Himmelstein, K.J. and Lutz, R.J. A Review of the Applications of Physiologically Based Pharmacokinetic Modeling. J. Pharmacokinetics and Biopharmaceutics, 7: 127-145, 1979.

Speyer, J.L., Collins, J.M., Dedrick, R.L., Brennan, M.F., Buckpitt, A.R., Londer, H., DeVita, V.T., Jr., and Myers, C.E.: Phase I and pharmacologic studies of 5-fluorouracil administered intraperitoneally. Cancer Research 40: 567-572, 1980.

Speyer, J.L., Sugarbaker, P.H., Collins, J.M., Dedrick, R.L., Klecker, R.W., Jr., DeVita, V.T., Jr., and Myers, C.E.: Portal uptake and hepatic metabolism of 5-fluorouracil (5-FU) administered by intraperitoneal (ip) dialysis (abstract). Proc. Am. Assoc. Cancer Research 21: 158, 1980.

Ozols, R.F., Young, R.C., Speyer, J.L., Weltz, M., Collins, J.M., Dedrick, R.L., and Myers, C.E.: Intraperitoneal (IP) adriamycin (ADR) in ovarian carcinoma (OC) (abstract). Proc. Am. Soc. Clin. Oncology 21: 425, 1980.

Collins, J.M., Dedrick, R.L., King, F.G., Speyer, J.L. and Myers, C.E.: Nonlinear pharmacokinetic models for 5-fluorouracil in man: intravenous and intraperitoneal routes. Clin. Pharmacol. Therap. 28: 235-246, 1980.

Collins, J.M. and Dedrick, R.L.: Pharmacokinetics of anticancer drugs. In Clinical Pharmacology of Antitumor Drugs, B.A. Chabner (Ed.), Saunders, Philadelphia (In press).

Lutz, R.J., Dedrick, R.L. and Zaharko, D.S.: Physiological pharmacokinetics: an in vivo approach to membrane transport. J. Pharmacol. Therapeutics (In press).

> Reprinted in International Encylopedia of Pharmacology and Therapeutics, Membrane Transport of Chemotherapeutic Agents, I.D. Goldman (Ed.), Pergamon, New York (In press).

King, F.G. and Dedrick, R.L.: Pharmacokinetic model for 2-amino-1,3,4-thiadiazole in mouse, dog, and monkey. Cancer Treatment Rep. 63: 1939-1947, 1979.

Speyer, J.L., Sugarbaker, P.H., Collins, J.M., Dedrick, R.L., et al.: Portal levels of hepatic clearance of 5-fluorouracil after intraperitoneal administration in man. Cancer Research (In press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 10002-15 BE

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Implant Device Development

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.W. Boretos	Physical Scientist	BEIB DRS
OTHER:	C.L. McIntosh	Senior Surgeon	SU NHLBI
	W.S. Pierce	Associate Professor	Penn. State Univ.
	J. Doppman	Radiologist	DR CC

COOPERATING UNITS (if any)

SU-NHLBI; DR-CC; Pennsylvania State University

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	1.7	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of the project is to elucidate the interaction of biomaterials used for specific implants with the physiological environment and to explore specially prepared materials and design features with respect to their suitability and performance in a variety of contexts. After removal from the host organism, implants will be examined for lipid absorption, calcium and/or protein deposition, changes in surface-free energy, and alteration of physical properties. Prostheses such as artificial hearts, heart valves and catheters will be employed. Observations should include scanning electron microscopy (SEM), infrared spectroscopy, contact angle measurements, and energy dispersive X-ray analysis. Physical measurements will be made of tensile properties, flexural-fatigue resistance, electrical properties, hardness, density, coefficient of static and kinetic friction, hydrophilicity, and other surface and bulk properties.

PHS-6040
(Rev. 10-76)

Objectives: Elucidate the interaction of polymers, metals, and ceramics used for specific implants with the physiological environment; explore specially prepared polymers and design features with respect to their suitability and performance in a variety of contexts.

Methods Employed: Basic composition of the biomaterials is carefully controlled, and modifications are employed to enhance acceptability by the living system. After removal, implants are examined for lipid absorption, protein and/or calcium deposition, changes in surface-free energy, and alteration of physical properties. Observation techniques include SEM, infrared spectroscopy, contact angle measurements, energy dispersive X-ray analysis, and atomic absorption spectroscopy. Flow characteristics and pressure gradients across heart valve implants are studied *in vitro* in a test apparatus. Electronic implants are examined periodically *in vivo* for changes in threshold levels, corrosion, and tissue reactivity. *In vitro* studies of the aforementioned are designed to accelerate fatigue testing and methods of improvement through heat treatment of the metal components undergoing stress. Surfaces of catheters are modified using surface treatments of grafted polymers and copolymers to reduce drag through the blood vessels. These catheters are tested for burst strength, stiffness, tensile strength, and density. The basic composition is modified through compounding. Embolizing agents consisting of composites of polymers, ceramics, and metals are being devised for delivery through the catheter systems so as to block arteries and vessels in the treatment of lesions such as aneurysms and arteriovenous malformations.

Major Findings: A number of forms and compositions of embolizing agents implanted in cats and monkeys have proven to be unsatisfactory due to localized tissue reactivity.

Tensile properties of selected polyurethanes can be significantly enhanced for implant use through a controlled annealing process.

Perfusion of drugs through micro-catheters can be determined through a calibrated capillary as a function of viscosity and pressure.

Significance: Physiologically compatible polymers with enduring strength are needed for such applications as heart valves, heart-assist devices, vascular implants, indwelling catheters, and subcutaneous uses.

Proposed Course: Extend experimental studies to further characterize the surface and bulk properties of biomaterials and, more specifically, determine their interactions with blood and subcutaneous tissue to facilitate development of better surgical implants.

Publications:

Boretos, J.W.: Encapsulation considerations for acute/long term durability of electronic implants. In M. Szycher and W.I. Robinson (Eds.) *Synthetic Biomedical Polymers: Concepts and Practice*, Technomics, Inc., Westport, Conn. (In press).

Boretos, J.W.: Polymers for implantable telemetry devices. Proceedings of workshop on "Implantable Transducers and Systems: Packaging Methods and Testing Criteria." Stanford University, June 27-29, 1979.

Boretos, J.W.: The chemistry and biocompatibility of specific polyurethane systems for medical use. In D.F. Williams (Ed.) Biocompatibility of Clinical Implant Materials, CRC Press (In press).

Boretos, J.W.: Past, present and future role of polyurethanes for surgical implants. J. Pure and Applied Chemistry 52: 1851, 1980.

Boretos, J.W., Terek, R.M., Girton, M.E. and Doppman, J.L.: Cohesive and frictional reduction of intra-arterial micro-catheters. Proceedings of the 33rd Annual Conference on Engineering in Medicine and Biology, Washington, DC, Sept. 1980 (In press).

Boretos, J.W., Dengler, W.C., Terek, R.M., Edwards, K.J., Jr., Wilkins, J.F., Girton, M.E., and Doppman, J.L.: Integral balloon catheter for interventional radiology. Proceedings of the 33rd Annual Conference on Engineering in Medicine and Biology, Washington, DC, Sept., 1980 (In press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 10007-06 BEI

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Investigation of Oxidative Metabolism and Potassium Kinetics in the Cat Brain

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W.H. Schuette	Chief	ACES BEIB DRS
OTHER:	B.A. Vern	Clinical Associate	CNB NINCDS
	W.C. Whitehouse	Electronics Technician	ADM CC
	N. Mutsuga	Visiting Fellow	CNB NINCDS

COOPERATING UNITS (if any)

CNB-NINCDS; AB-CC

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Applied Clinical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.0	2.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ [✓ (c) NEITHER]

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Oxidative metabolism, as indicated by the fluorescence of nicotinamide adenine dinucleotide (NADH) and oxygen consumption, was assessed to investigate potassium ion kinetics in the cat brain. Research was conducted to determine if the potassium clearance process is active or passive after activation of the cortex. Investigations were also conducted to determine the applicability of the NADH fluorescence technique to exposed myocardium. Active work on this project was completed before September 30, 1977; two papers were published subsequently in 1979 listed last year and an additional paper this year.

Methods Employed: The NADH fluorescence at 470 nM is excited by illumination with ultraviolet light at 360 nM obtained from a high pressure Hg arc lamp. To compensate for blood volume changes within the field of interest, we developed and used a television fluorometer employing fluorescein dye as a reference. The technique, initially used for study of cat brain, was also applied successfully to exposed myocardium.

A potassium-sensitive microelectrode system was employed for measuring both extracellular and intravenous potassium ion levels.

Direct cortical oxygen consumption measurements were made by cannulation of the sagittal sinus and monitoring the flow rate and hemoglobin saturation of the blood flowing out of the sinus. The calculated oxygen consumption is proportional to the arterial-venous oxygen concentration difference multiplied by the flow rate.

For the Q_{10} experiments, the exposed cat hippocampus temperature was either elevated or lowered by use of a controlled temperature stream of artificial spinal fluid which flowed over the surface of the hippocampus. Surface temperature was monitored by a small thermistor probe.

Major Findings: The NADH dynamics observed in the myocardium are similar to those observed in the cortex.

Blood volume in transiently ischemic myocardial tissue may increase due to relaxed muscle tone.

Fluorescein fluorescence was found to be an excellent indicator of myocardial perfusion.

Agreement was found between an analytical model for potassium clearance and experimentally determined potassium kinetics. This agreement provided further evidence of the active clearance process previously suggested by Q_{10} measurements and the slowing of potassium clearance during periods of hypotension.

Publications:

Vern, B.A., Schuette, W.H., Mutsuga, N., and Whitehouse, W.C.: Effects of ischemia on the removal of extracellular potassium in cat cortex during pentylenetetrazol seizures. Epilepsia, 20: 711-724, 1979.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 10011-06 BEI

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Electrical Safety Program for Clinical Center Patients and Patient Care and Treatment Areas

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. Corsey	Electronic Engineer	BEIB DRS
OTHER:	W. Schuette	Chief	ACES BEIB DRS
	C. Strong	Environ. Services Officer	CC
	T. Johnson	Administrative Officer	CC
	J. Bucolo	Electronic Technician	BEIB DRS
	W. Connoley	Super. Electronic Tech.	BEIB DRS

COOPERATING UNITS (if any)

ADM-CC; CCIS-BEIB

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Applied Clinical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 1.0	PROFESSIONAL:	OTHER: 1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The electrical safety program assures a hazard-free electrical environment for Clinical Center patients by testing clinical electrical equipment on a regular basis, investigating electrical shocks in patient areas, providing instruction to Clinical Center and Division of Safety personnel, assuming compliance with standards of the Joint Commission on Accreditation of Hospitals and the National Electric Code, participation in Clinical Center committees relating to medical equipment, inspecting new construction and renovation, design and modification to test equipment and participation in the formulation of national standards.

Objectives: To eliminate electrical shock hazards from Clinical Center patient areas; to assure Clinical Center compliance with requirements for accreditation; to participate in activities of the Clinical Center Safety Committee and the Medical Device Evaluation and Standardization Committee; to investigate electrical shocks and burns and recommend corrective action; to inspect new and renovated patient areas for proper grouding and electrical service; to take an active role in formulation of national electrical safety standards.

Major Findings: (1) Several areas of the Clinical Center contained ungrounded 250 volt receptacles which met code requirements when installed, but are considered hazardous by todays standards. (2) Clinical electrical equipment are in need of a preventative maintenance program to promote performance assurance and reduce equipment failures. (3) Clinical Center defibrillators are in need of a scheduled program of testing to assure their readiness for emergency use. The testing being performed presently is not sufficient and not all defibrillators are tested regularly.

Proposed Course: (1) To eliminate from the Clinical Center all ungrounded 250 volt receptacles and educate personnel regarding the hazard involved in their use. (2) To initiate a formal preventative maintenance program for performance assurance of clinical electrical equipment. The program should also reduce down time and failure rates. The equipment would be evaluated on an annual basis. (3) To establish a formal testing program for defibrillators with weekly testing of battery powered defibrillators and quarterly testing of line powered defibrillators.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 10015-05 BEI

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Development of Miniature Catheter for Clinical Use

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S.R. Goldstein	Mechanical Engineer	BEIB DRS
OTHER:	J.L. Doppman	Chief	DR CC

COOPERATING UNITS (if any)

DR-CC

LAB/BRANCH

Biomedical Engineering and Instrumentation Branch

SECTION

Mechanical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, MD 20205

TOTAL MANYEARS: .5	PROFESSIONAL: .25	OTHER: .25

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A miniature toposcopic catheter attached to the end of a 1-mm #6 French catheter has been developed for insertion in tortuous blood vessels as small as 1 mm in diameter and up to 30 cm long. Catheter tests in anesthetized dogs have been highly successful - the catheter is able to penetrate parts of the vascular system which are unaccessible by existing techniques. The apparatus has been redesigned to provide the reliability and convenience required for clinical use. The catheter will enable the delivery of embolizing agents or other therapeutic substances so that some procedures previously requiring surgery can be performed instead with catheters. Techniques of steering the catheter are being developed and efforts are in progress to reduce the outer catheter size to #5 French and allow aspiration of fluid from remote areas.

PHS-6040
(Rev. 10-76)

Objectives: Develop techniques and devices for inserting a miniature catheter into small tortuous vessels and steering it into selected branches.

Develop techniques and devices for delivering therapeutic materials into the catheterized vessel for clinical usage and to aspirate fluids from these locations.

Major Findings: A miniature topographic catheter capable of negotiating tortuous paths has been successfully tested in dogs and will soon be ready for clinical use.

Significance: Surgeons and radiologists have long sought techniques for catheterizing small diameter vessels separated from larger, easily catheterized vessels by long, narrow passages with numerous bifurcations. The capability would permit selective treatment of tumors, aneurysms, and other lesions with minimal danger to normal tissues. Delivery of embolizing agents and materials to stain tissue, as well as aspiration of fluid, are contemplated.

Proposed Course: Complete construction and testing of the clinical apparatus and then use the system clinically. Develop steering techniques, test in animals, and incorporate into the existing system. Develop related devices and explore additional used for the catheter.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10018-05 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Particulate Hydrodynamics in Porous Membranes

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P.M. Bungay	Chemical Engineer	BEIB DRS
	M.E. O'Neill	Reader Mathematics	Univ. Coll., London

COOPERATING UNITS (if any)

Department of Mathematics, University College, London

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.2	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Mathematical models are being developed to describe passive membrane transport through pores or intracellular gap junctions. The Taylor-Aris dispersion analysis is extended to treat combined Brownian motion and convection in a single pore. The solute particle dimension is assumed to be large compared to that of the solvent molecules and also appreciable in size compared to that of the solvent molecules and also appreciable in size compared to the lateral pore dimension. The latter condition implies strong "hindered diffusion" and related solute-membrane interaction effects. A key aspect of the analysis is a generalized Einstein relation for predicting axial and radial components of the diffusivity tensor from hydrodynamics solutions for resistance coefficients. Perturbation techniques are used to obtain asymptomatic solutions to the hydrodynamic equations, and the method of moments is employed to analyze the solute continuity equation. Related hydrodynamic problems are also being considered, such as flow through constricted vessels.

PHS-6040
(Rev. 10-76)

Objectives: The objective of this project is to provide the basis for a rigorous, predictive continuum theory for passive transport phenomena in porous membranes, including such observations as "hindered diffusion". The development of solutions to hydrodynamic problems of interest in other areas of the biological and physical sciences is also considered.

Methods Employed: The essence of the approach to membrane transport is an extension of the Einstein continuum analysis for the Brownian motion of spherical molecules in dilute solutions. Einstein derived his predictive relation for the diffusion coefficient from the theoretical expression for the hydrodynamic resistance to translation of a rigid sphere through a homogenous viscous fluid of infinite extent. The continuum analysis for porous membranes begins with a single solute molecule in a single pore and assumes that the form of Einstein's relationship between the diffusion and resistance coefficients remains valid. However, the presence of the rigid pore wall, in general, increases the hydrodynamic resistance to translation and rotation of the solute relative to the fluid. The diffusivity is thereby decreased in magnitude until, in the limit, as the solute dimension becomes equal to the lateral pore dimension, the diffusion coefficient falls to zero. Where there is, in addition to diffusion, net movement of the fluid through the pore, the hydrodynamic interaction similarly affects the solute flux relative to the solvent flux. The project is concerned with deriving the requisite expressions for the resistance coefficients from hydrodynamic theory as well as developing analyses for diffusive and convective porous membrane transport.

The primary theoretical tools used in the hydrodynamic problems are regular and singular perturbation techniques (typically using the ratio of solute to pore dimensions as the asymptotic expansion parameter) and collocation techniques of the type developed by Weinbaum, and Pfeffer.

The transport analysis has been approached using the Taylor-Aris type dispersion treatment and the method of moments for deriving expressions for the pertinent coefficients without directly solving the complete solute continuity equation (convective-diffusion equation).

Major Findings: We completed the derivation of expressions correct to the second order in the sphere-to-tube radius ratio for the pressure drop due to the presence of neutral spherical solutes in cylindrical pores. Numerical computations using these expressions is proceeding.

An analysis was begun for describing the axisymmetric settling of a toroidal particle inside a vertical fluid-filled tube.

Proposed Course: In addition to the models presently under study, it would be desirable to examine a situation in which the solute is a nonspherical body in order to determine how to handle partical orientation and rotational Brownian motion effects. An ellipsoidal solute would be the likely choice in terms of posing theoretically tractable problems. Another direction to pursue, which would greatly extend the range of applications for the theory, would be to incorporate into the present models nonhydrodynamic solute-membrane interactions such as electrostatic or London Van der Waals attractive/repulsive forces.

Significance: Channels (pores, slitlike gap junctions) represent one important type of transmembrane transport in biological systems. A rigorous conceptual and predictive framework for pore theory would be useful in clarifying relevant biological transport and would find wide applicability in engineering and physical science work pertaining to synthetic membranes.

Publications:

Bungay, P.M. and O'Neill, M.E.: The pressure drop along a tube due to an axisymmetric constriction. J. Colloid Interface Science 71(2): 216-236, 1979.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 10022-04 BEI

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Fiber Optic Probes/pH Probe

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.I. Peterson	Chemist	BEIB DRS
OTHER:	S.R. Goldstein	Mechanical Engineer	BEIB DRS

COOPERATING UNITS (if any)

H-IR-MH

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Chemical and Mechanical Engineering Sections

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .25	PROFESSIONAL: .25	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

In the initial year of the project, a miniature pH sensor, based on fiber optics, was designed to pass through a 22-gauge needle intended for implantation in tissue for physiological studies during exercise. The operation of the probe depends on pH changes identified by dye indicators. The probe is connected to laboratory optical instrumentation.

During the second year, an electro-optic measuring and readout system was designed and developed specifically for the pH sensors. The new unit makes the overall system portable, practical, and easy to use. In vitro tests were performed to characterize the pH sensor and the instrument. In the third year, improvements in the probe were made, and its applicability to blood pH determination was shown.

The effort during the current year was on improvement in the probe, aid to investigators interested in its application, and preparation of a publication.

Objectives: Develop a pH sensor for tissue implantation to be used in studies of oxygen transport during exercise.

Methods Employed: A fiber optic measurement of dye indicator response to pH.

Significance: In studies of abnormality in transport of oxygen to tissue by blood during exercise, measurements of oxygen pressure in the tissue can be used to determine the oxygen content of the blood supply via the blood oxygen saturation curve (concentration vs. pressure). Alternately, measurements of the blood oxygen concentration can be used to determine oxygen pressure by this curve. Since the relation between oxygen pressure and concentration is affected by changes in pH which occur during exercise (shift in the curve with pH, the Bohr effect), it is necessary to incorporate a pH measurement with the oxygen measurement in making use of the curve.

The probe is also potentially useful for clinical application in monitoring blood and tissue pH in heart surgery and other intensive care situations.

Publications:

Peterson, J.I., Goldstein, S.R., Fitzgerald, R.V. and Buckhold, D.K.: A fiber optic pH probe for physiological use. Analytical Chemistry 52: 864, 1980.

Goldstein, S.R., Peterson, J.I. and Fitzgerald, R.V.: A miniature fiber optic pH sensor for physiological use. ASME Transactions, Journal of Biomechanical Engineering 102: 141, 1980.

Further work on the pH probe is not planned.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 10023-04 BEI

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Two-Dimensional Ultrasonic Imaging System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W.H. Schuette	Chief	ACES BEIB DRS
OTHER:	W.S. Friauf	Chief	EEES BEIB DRS
	T.E. Hall	Electronic Engineer	BEIB DRS
	J.L. Doppman	Chief	DR CC
	T.H. Shawker	Clinical Associate	DR CC
	W.C. Whitehouse	Electronic Technician	ADM CC

COOPERATING UNITS (if any)

DR-CC; ADM-CC

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Applied Clinical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.0	2.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ [✓ (c)] NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Several subsystems of a comprehensive, versatile, ultrasonic imaging and recording system have been developed. A second-generation real-time mechanical sector scanner has been put into use along with a video system for consolidation, displaying, and recording a variety of data. The development of a solid-state sector-to-TV scan converter is completed. The overall system has proved to be especially useful in abdominal scanning and early detection of pregnancy. It is now also being employed for tongue motion in a voice study.

PHS-6040
(Rev. 10-76)

Objectives: Development of a high-performance two-dimension real-time ultrasonic imaging system with provision for a standard TV output to facilitate video tape recording of an examination, including the sector, a view of the patient, real-time clock, additional alpha numeric information, moving trace ECG and pressure data, voice commentary. Additional objectives are versatility, that is, suitability for ocular, cardiac, pediatric, and abdominal scanning with minor changes, and high benefit/cost ratio.

Methods Employed: Based on the positive results obtained with the mechanical scanner designed and built earlier, a second-generation mechanical sector scanner was developed. The size of the scanner and mechanical vibration have been substantially reduced. In addition, the new scanner maintains electrical control of the scan pattern through the use of position feedback, which provides three major advantages relative to earlier mechanical scanners: (a) lines are spaced uniformly throughout the sector; (b) synchronization with standard TV systems is easy--a feature which facilitates high-quality imaging in video format.

For the purpose of building up a TV picture with many types of information simultaneously for recording via video tape, appropriate commercial components have been assembled into a system.

Publications:

Dunnick, N.R., Schuette, W.H. and Shawker, T.H.: Ultrasonic demonstration of thrombus in the common carotid artery. AJR 133, 544-545, September, 1979.

Shawker, T.H., Schuette, W.H., Whitehouse, W., and Rifka, S.M.: Early fetal movement: A real-time ultrasound study. Obstetrics and Gynecology, Vol. 55(2), February, 1980.

Shawker, T.H., Schuette, W.H. and Whitehouse, W.: Overhead TV camera: Useful addition to ultrasonic laboratory. AJR 134: 608-609, March, 1980.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 10027-04 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Development of Whole-Body Hyperthermia Instrumentation and Control System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W.H. Schuette	Chief	ACES BEIB DRS
OTHER:	J. Bull	Senior Investigator	MC DCT NCI
	D. Lees	Staff Anesthesia	CC NIH
	J. Whang Peng	Senior Investigator	MS DCT NCI
	R. Corsey	Electronic Engineer	BEIB DRS
	H. Tipton	Mechanical Engineer	BEIB DRS

COOPERATING UNITS (if any)

MC-DCT-NCI; CC-NIH; MS-DCT-NIH

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Applied Clinical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3	2	1

CHECK APPROPRIATE BOX(ES)

☐ X(a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Whole body hyperthermia is being studied at NIH as a possible means of treatment for cancer. This project includes development of an instrumentation and control ssytem based on utilization of a Tektronix 31 programmable calculator, digital plotter, and interface for data acquisition. The esophageal temperature of the patient is regulated to 0.1°C accuracy by feedback control of the temperature of water circulating in a set of hyperthermia blankets. This project was comleted August 1980, however additional publications have been made.

PHS-6040
(Rev. 10-76)

Methods Employed: A Tektronix 31 programmable calculator is being used to acquire, record, and process data as well as to control water temperature of a set of hyperthermia blankets. The temperature of the water pumped through the blankets together with esophageal and rectal temperatures of the patient are processed by the calculator, which then develops temperature commands for the water temperature mixing valve. The mixing valve adds hot or cold water to the flow stream returning from the blankets as directed by the Tektronix digital interface unit so that heart rate, blood pressure, and temperature data could be processed by the system. The multiplexer module also provides commands from the calculator to the water mixing valve motor. Automatic cool-downs are programmed into the calculator in response to various out-of-limit conditions. The calculator functions in an interactive mode for entry of operational instructions.

Major Findings: The major finding from the use of the equipment is that it is possible to take the whole-body core temperature of patients to 42.0 ±0.1°C for four hours on a biweekly basis without major difficulty. The finding suggests that hyperthermia treatment for cancer is practical. Currently, the system is being employed in conjunction with chemotherapy.

Publications:

Bistoni, F., Lees, D.E., Bull, J.M., Baskies, A.M., Chretien, P.B., Smith, R., Whang-Peng, J., Schuette, W.H. and DeVita, V.T. Correlation of Serum Glycoproteins and Blood T-cell Levels with Clinical Course During Whole Body Hyperthermia (WBHT) Alone or with Chemotherapy. Proceedings of 15th American Society Clinical Oncology, New Orleans, May 14-15, 1979, p. 194.

Bull, J.M., Whang-Peng, J., Lees, D.E., Smith, R., Schuette, W.H., Kim, Y.D., DeVita, V.E. Phase I Trial of Systemic Heat and Adriamycin. Proceedings of 15th American Society Clinical Oncology, New Orleans, May 14-15, 1979, p. 398.

Kim, Y.D., Lees, D.E., Lake, C.R., Whang-Peng, J., Schuette, W.H., Smith, R., and Bull, J. Hyperthermia Potentiates Doxorubicin-Related Cardiotoxic Effects. JAMA 241(17), April 27, 1979.

Lees, D.E., Kim, Y.D., Schuette, W.H. and Macnamara, T.E. Auscultatory Confirmation of Placement of Esophageal Temperature Probe. Anes. Rev. 35, August, 1979.

Kim, Y.D., Lake, R., Lees, D.E., Schuette, W.H., Bull, J.M., Weise, V., and Kopin, I.J.: Hemodynamic and Plasma Catecholamine Responses to Hyperthermic Cancer Therapy in Humans. American Journal of Physiology 237(5), pp. H570-H574, 1979.

Lees, D.E. and Schuette, W.H.: Microwave Rewarming. Anesthesia and Analgesia, Vol. 59(2), 161, 1980.

Lees, D.E., Kim, Y.D., Bull, J.M., Whang-Peng, J., Schuette, W., Smith, R., and Macnamara, T.E.: Anesthetic Management of Whole-Body Hyperthermia for the Treatment of Cancer. Anesthesiology 52: 418-428, 1980.

Bull, J.M., Lees, D.E., Smith, R., Schuette, W.H., Katin, M., Glatstein, E., and Devita, V.T.: Whole Body Hyperthermia (WBH) Combined with Nitrosourea in Malignant Melanoma. Proc. ASCO Meeting, March, 1980, San Diego, CA.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 10034-03 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Three-Dimensional Histological Reconstruction

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S.B. Leighton	Mechanical Engineer	BEIB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.5	.45	.05

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A semi-automatic system for acquisition of three-dimensional structural information about histological material is being developed. The system should have significant speed and reliability advantages over present techniques using serial sections, although resolution may be limited. In brief, an embedded tissue block will be fixed relative to a scanning electron microscope imaging system, the surface of the block will be imaged and stored, and successive slices will be removed by a built-in microtome. Handling and registration of thin sections will thus be eliminated. Human and computer pattern recognition will transform the resulting set of images into a three-dimensional reconstruction.

PHS-6040
(Rev. 10-76)

Objectives: (1) To facilitate making schematic diagrams of neural nets. (2) To facilitate developmental studies of small organs and organisms.

Methods Employed: Various cutting, staining, and imaging techniques are being evaluated for best resolution.

Major Findings: So far, the feasibility of the project has been demonstrated in that resolution of 600 Angstroms has been achieved on cut faces of Epon embedded neural material in the SEM. Construction of the miniature microtome is complete.

Significance: Neuroanatomists may be able to trace significant neural nets easily enough to do enough samples to be statistically significant.

Proposed Course: The miniature microtome will be bench tested to verify proper cutting mechanics and general operation. The unit will be integrated with a scanning electron microscope and cutting will be tested in a vacuum. Finally, the entire system will be integrated with a computer for semi-automatic reconstructions.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 10039-03 BEI

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Biophysical Instrumentation and Methodology

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M.S. Lewis	Research Chemist	BEIB DRS
OTHER:	T.R. Clem	Electronics Engineer	BEIB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Office of the Chief

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DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.2	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ [✓ (c)] NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The project is designed to develop new instrumentation and methodology or improve existing instrumentation and methodology for characterization of biological macromolecules. Analytical ultracentrifugation and techniques ancillary to it are the major areas of interest.

Objectives: To develop data acquisition systems for analytical ultracentrifuges and for ancillary equipment such as plate or film readers and densimeters and to develop appropriate software to use with the acquisition systems.

Methods Employed: A microprocessor controlled data acquisition system has been developed for use with the Anton Paar densimeter which is used for the determination of solution densities needed for the calculation of partial specific volumes required for the determination of molecular weights from ultracentrifuge data. This acquisition system controls the operation of the densimeter, records data acquired from it, calculates current means and standard deviations and prints all of these values. Thus, once a sample has been introduced into the instrument, operation is entirely automatic until the investigator, on the basis of the printed values of the means and standard deviations, decides that the measurement has been made to the desired level of precision. This has simultaneously resulted in increasing the attained level of precision and in greatly reducing the amount of time the investigator has to spend in obtaining good data. Microprocessor controlled data acquisition systems for the analytical ultracentrifuge and for the plate and film reader used with the ultracentrifuge are presently under development. These will be controlled by a microcomputer which will also be used to store data, do preliminary calculations and editing, and then transmit the data to the DEC-10 computer for further processing which would be beyond the capabilities of the microcomputer.

Significance: The data acquisition system for the densimeter has already greatly facilitated the use of this instrument, resulting in the greatly improved acquisition of data from this instrument with a very marked diminution in the time required of the investigator and a significant improvement in the precision of the densities obtained. Since data acquisition has been the limiting factor in terms of the qualitative and quantitative aspects of ultracentrifuge research, it is anticipated that the development of the data acquisition systems described above will greatly facilitate such research.

Proposed Course: Continue the developments outlined above.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 10040-03 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Physical Chemistry of Biological Macromolecules

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M.S. Lewis	Research Chemist	BEIB DRS
OTHER:	R.S. Adelstein	Section Chief	CB NHLBI
	S.I. Chung	Research Chemist	LB NIDR
	G. Felsenfeld	Section Chief	LMB NIAMDD
	J.S. Finlayson	Director	PDB BB
	J.A. Gladner	Research Chemist	LCB NIAMDD
	A.P. Minton	Research Chemist	LCB NIAMDD
	J.C. Osborne	Research Chemist	MD NHLBI
	R. Shrager	Mathematician	LSMM DCRT
	J. Waters	Physical Sciences Aide	BEIB DRS

COOPERATING UNITS (if any)

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Office of the Chief

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 1.1	PROFESSIONAL: 0.9	OTHER: 0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES x☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to study the physical properties of a wide variety of biological macromolecules with the goal of correlating these properties to the structure and function of the macromolecules. The emphasis is on molecular size and shape, the thermodynamics of molecular interactions, and on molecular weight distributions. Analytical ultracentrifugation and mathematical modelling are the principal research techniques used.

Objectives: (1) To study the ultracentrifugal behavior of myosin phosphatase. (2) To study the anomalous partial specific volume of lamprey fibrinogen in 6 molar guanidine hydrochloride buffer. (3) To study the nature of density gradients of high concentrations of dextrans in the ultracentrifuge. (4) To study the ultracentrifugal behavior of the D-fragment of human fibrinogen. (5) To study the ultracentrifugal behavior of hemoglobin and myoglobin at physiological concentrations. (6) To study the effects of surface activity on solute distribution in the ultracentrifuge. (7) To study the effectiveness of mathematical modelling in discriminating between correct and impostor models for fitting ultracentrifuge data. (8) To study methods for the analysis of molecular weight distributions from ultracentrifuge data.

Methods Employed: The various macromolecules have been isolated and purified from appropriate sources by conventional means or have been prepared synthetically. The molecular weights have been determined by analytical ultracentrifugation and the resultant data has been analyzed by mathematical modelling techniques using the MLAB system on the DEC-10 computer. Mathematical modeling techniques have also been used for studies of molecular weight distribution and for studies on fitting ultracentrifuge data. Partial specific volumes have been studied by densimetric techniques.

Major Findings: Preliminary studies on myosin phosphatase appear to indicate that this enzyme undergoes a reversible association as a monomer-dimer-tetramer. Studies are now underway to investigate this possibility and to determine the thermodynamic parameters of the association.

Studies on lamprey fibrinogen indicated that the partial specific volume of this macromolecule changed in an anomalous manner when the fibrinogen was dissolved in 6 molar guanidine buffer. This change was deduced from ultracentrifugal data. It is now being verified by densimetric studies which directly measure the partial specific volume of the fibrinogen in normal buffers and in 6 molar guanidine buffers.

The ultracentrifugal density gradients of various dextrans as functions of loading concentration and rotor speed were determined. This required the measurement of concentration distributions of high concentrations of dextrans and also densimetric measurement of the partial specific volumes of the dextrans. Equations were derived which would accurately predict the densities of the different dextrans as functions of position in the ultracentrifuge cell given the loading concentration, the rotor speed, and the positions of the solution meniscus and bottom in the cell.

Studies on the D-fragment of human fibrinogen show that preparations which have not been in contact with any denaturing solvents such as high concentrations of urea of guanidine are homogenous, do not exhibit any aggregative behavior, and have a molecular weight of 120,000 daltons.

The ultracentrifugal behavior of myoglobin and hemoglobin at very high concentrations has been studied in order to determine whether or not myoglobin undergoes any associative reaction at physiological concentrations. The very great optical densities of such solutions which were at concentrations as high as 35% required devising 0.1 mm thick centerpieces for the ultracentrifuge cells. The problem of possible association of the myoglobin being masked by the marked thermodynamic non-ideality at high concentrations was treated by studying the ratios of the apparent molecular weights of myoglobin and hemoglobin as functions of concentration, since both are hemoproteins with very similar monomer molecular weights and the associative behavior of hemoglobin is well known. The data strongly suggests that myoglobin associates at least to form a dimer and that further association might be possible. Additional studies are being planned to further elucidate this possible association.

Studies on plasma apolipoproteins showed that they exhibited a significant level of surface activity and also that this surface activity might result in anomalies of concentration distribution in the ultracentrifuge cell. A thermodynamic theory for the effect of surface activity on concentration distribution was derived and mathematical modelling showed that the effect was of a significant magnitude under certain experimental conditions. The application of this theory to the experimental data is now in progress.

Mathematical modelling has been used to determine how well this technique can be used to determine an appropriate model of an associating system. This has been done by generating simulated data for a specific model, adding experimental noise, and then comparing the fits of the correct model and of imposter models. It has been shown that in almost all cases, if the experiment is properly designed, it is possible to discriminate between correct and impostor models. This study has been useful also in determining the factors in experimental design which optimize the discrimination between models.

Studies on obtaining molecular weight distributions from ultracentrifugal data have involved determination of the necessary criteria for obtaining these distributions using regularization techniques. In spite of having some success in fitting symmetrical and skewed unimodal distributions, the lack of success we have had in fitting any more complex distributions has convinced us that this problem is mathematically too ill-conditioned for this approach to succeed. We are now attempting to determine whether it is possible to determine a distribution by comparing the concentration distribution associated with a particular molecular weight distribution with an experimentally obtained concentration distribution using the criteria found appliable in the studies on associating systems.

Significance: The studies on the fibrinogens and their fragments are relevant to a basic understanding of their antigenicity and to the action of plasmin on fibrinogen; these all relate to the role of fibrinogen in normal and pathological blood clotting. The studies on myosin phosphorylase are relevant to the role of this enzyme to the mechanism of myosin in muscle concentration. The studies on the density distributions of dextrans is significant because these are used in ultracentrifugal studies of the physical properties of nucleosomes. The studies on the surface properties of the plasma apolipoproteins are relevant to the interaction of these proteins with plasma lipids. The studies of myoglobin at high concentrations is relevant to the behavior of the oxygen-binding hemeproteins at physiological concentrations. The mathematical modelling studies are of importance because they enhance our abilities to successfully deal with these problems in the physical chemistry of macromolecules.

Proposed Course: The manuscript on lamprey fibrinogen will be revised to incorporate the new data on partial specific volumes. Manuscripts on the effects of surface activity of plasma apolipoproteins, on mathematical modelling studies on associating systems, and on the behavior of myoglobin at physiological concentrations have been started. Further studies on myoglobin, fibrinogens, and on myosin phosphorylase are planned. The mathematical modelling studies on molecular weight distributions will be continued. New studies on modified hemoglobins, natural and synthetic detergents, and on various protein interactions are planned.

Publications:

Davies, P.J.A., Wallach, D., Willingham, M., Pastan, I., and Lewis, M.S.: Self-association of chicken gizzard filamin and heavy merofilamin. Biochemistry 19, 1366-1372, 1980.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 10041-03 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Flow Visualization Studies and Hemodynamic Events in Model Arteries

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.J. Lutz	Chemical Engineer	BEIB DRS
OTHER:	R.L. Dedrick	Chief	ChES BEIB DRS
	D.L. Fry	Chief	H IR OD

COOPERATING UNITS (if any)

OD - IR - NHLBI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.7	0.4	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The appearance of atherosclerotic lesions at specific locations in the arterial tree has led many investigators to study the relevance of hemodynamic factors in atherogenesis. The purpose of this study is to investigate the patterns of flow in models of arterial geometry to measure velocity profile at several cross sections, and to seek correlations between fluid mechanic events and the development of atherosclerotic plaques. In previous studies, quantitative measurements of the wall shear stress were made in model arteries by an electrochemical technique. However, the work provided no information about the direction of the shearing forces, and little idea about the nature of the flow patterns. In this study various methods of flow visualization such as dye injection, neutrally buoyant microsphere tracers and laser illuminated light scattering particles are being used to study the flow patterns in arterial models as a function of various flow parameters such as Reynolds number, branch flow ratios, and pulsatility. Both still photography and high-speed cinematography record the flow phenomena. The electrochemical technique measures average mass transfer coefficients to the artery wall under conditions of steady and pulsatile flow.

Objectives: The objectives of this study are to visualize and record the various kinds of flow phenomena such as flow separation and secondary flow that may occur in complex flow channels that represent arterial geometry and to correlate the flow phenomena with the location of atherosclerotic plaques in experimental animals. The analysis will include a quantitative measure of the velocity profiles at various sites in the model arteries. In conjunction with these experiments, measurements will be made of the mass transfer coefficients to the walls of the model arteries under conditions of both steady and pulsatile flow.

Methods Employed: Several methods have already been shown to be useful for visualizing flow patterns in our model systems, and other methods can be tried. The electrochemical method of measuring mass transfer coefficients is being used in several model systems. The following techniques are being used.

(1) Dye injection. At selected sites in the arterial model, small ports are drilled for insertion of #30 gauge hypodermic tubing, which is connected via PE 10 catheter tubing to a reservoir of colored dye. The end of the hypodermic tubing can be positioned at any radial location in the flow model and the dye slowly injected into the flow to mark the streamlines. The streamline patterns at several sites are then recorded using 35-mm still photography. Data obtained by dye injection into the flow indicates that the flow streamlines are skewed toward the side-arm branches exiting from the main (aortic) flow channel and that unusual patterns of backflow and secondary flow occur near the dorsal channel wall just opposite the branch orifices. These phenomena are governed by the fraction of the flow that exits out each daughter branch.

(2) Neutrally buoyant microspheres. This method employs a dilute suspension of 100- to 500-micron diameter polystyrene microspheres in a 20 to 25 percent glycerine/water solution, which serves as the test fluid in the flow model. The microspheres are dyed with a fluorescent dye and then illuminated with ultraviolet light making them clearly visible in the flow system. The path of the microspheres are photographed with high-speed cinematography as these neutrally buoyant particles move along with the fluid. In such a manner, the direction and velocity of fluid elements can be determined. This method gives an overall view of the flow patterns throughout the bulk of the fluid flow.

(3) Laser Doppler velocimetry. When light is scattered from a moving object, a stationary observer will see a change in the frequency of the scattered light (Doppler shift) proportional to the velocity of the object. This Doppler shift is used to measure the velocity of particles at various locations in the fluid. From the particle velocity, the fluid velocity is inferred. A laser is used as the light source because it is easily focused and coherent. This method allows us to determine, quantitatively, the velocity profiles at various positions in the arterial model. Numerous profiles have been recorded in both steady and sinusoidal flow at various flow rates.

By passing the thin collimated laser beam through a cylindrical lens, a source of plane illumination can be created which can be usd to visualize a specific narrow cross section in the flow channel by observing its light scattering effect from small particles that move with the fluid. This technique exhibits, in two dimensions, various flow patterns like stream lines and separation eddies.

Significance: Elucidation of the role of hemodynamics on the onset and development of atherosclerotic plaques is fundamental in the study of vascular disease. Certain biological evidence suggest that areas of increased plaque formation may correlate with areas frequently exposed to disturbed flow, for example, flow separation, or to relatively stable flow patterns that change direction and magnitude periodically throughout the day with varying metabolic and blood flow demands. This study should demonstrate various types of flow patterns that can occur in arterial systems as a function of changing flow parameters. Likewise, the mass transfer of blood borne constituents like oxygen or lipoproteins can be affected by the flow patterns in various regions near the artery wall. An imbalance in the mass transfer of these elements can cause either vascular damage or excess accumulation of lipids which can eventually lead to a pathological state in the artery wall.

Proposed Course: (1) Study the flow patterns in these models using the various techniques described above as a function of several flow parameters such as Reynolds number, branch flow ratio, and flow pulse frequency. (2) Correlate these findings with those of our previous experiments on wall shear stress in similar models. (3) Determine the mass transfer coefficients to the arterial wall as a function of various Schmidt numbers under conditions of steady and pulsatile flow. (4) Correlate all hemodynamic evidence with incidence of lesions in experimental animals.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 10043-03 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Fiber Optic Probes/Oxygen Probes

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.I. Peterson	Chemist	BEIB DRS
OTHER:	S.R. Goldstein	Mechanical Engineer	BEIB DRS

COOPERATING UNITS (if any)

H-IR-MH

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .75	PROFESSIONAL: .75	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Successful development of a fiber optic pH probe has provided a model for the construction of other probes, the most important being an oxygen probe. The original approach taken for development of an oxygen probe was to find or develop a suitable reversible color indicator. Our attempts were unsuccessful, so effort starting last year and continuing through this year has been on adaptation of the principle of fluorescence quenching by oxygen.

Objectives: Develop an oxygen sensor for tissue implantation to be used in studies of oxygen transport during exercise, and clinical Po_2 measurements.

Methods Employed: A fiber optic measurement of dye-indicator response to oxygen by fluorescence quenching.

Significance: Po_2 measurements are fundamental to understanding and control of oxygen transport in research and clinical investigations. Measurements on withdrawn blood samples lack convenience, reliability, and relevance to many situations of interest. Indirect estimation of Po_2 using spectrophotometric measurements of hemoglobin oxygenation and the concentration-pressure transfer function (blood oxygen saturation curve) is subject to too many uncertain variables. Development of a fiber optic Po_2 probe would represent a significant advance in the ability to directly measure blood and tissue oxygen. A satisfactory electrode for general use has never been developed, and the fiber optic approach offers some distinct advantages in small size, flexibility, and safety.

Major Findings and Proposed Course: Fluorescence or phosphorescence quenching by oxygen is one of the most sensitive techniques available for oxygen measurement, but it is not directly applicable to use in a fiber optic probe without the resolution of three major problems: (1) the availability of a dye which combines sufficient sensitivity with long wavelength (> 450nm) excitation; (2) a water-vapor insensitive support for the dye which maintains its sensitivity to oxygen; and (3) a suitable highly oxygen permeable hydrophobic envelope for the probe. These problems have been solved, although there is room for improvement in item 2, the support. Current and continuing work is devoted to evaluation of probes constructed on this basis.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10050-02 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Positron Emission Tomography Scanner

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G. DiChiro	Section Chief	SN NINCDS
OTHER:	R.A. Brooks	Senior Staff Fellow	SN NINCDS
	V.J. Sank	Research Physicist	SN NINCDS
	W.S. Friauf	Electronics Engineer	EEESBEIBDRS
	S.L. Leighton	Mechanical Engineer	MES BEIB DRS
	H.E. Cascio	Electronics Engineer	EEESBEIBDRS
	G.L. Hemphill	Electronics Technician	EEESBEIBDRS

COOPERATING UNITS (if any)

SN NINCDS

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
EEES, MES

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 3.0	PROFESSIONAL: 2.7	OTHER:

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A custom PET scanner is being developed to provide compromises between resolution, sensitivity, count rate capability, and cost that are optimal for human neurological research requirements at NIH.

Objectives: Design and have built a PET scanner with higher resolution than other custom or commercial machines, but without excessive compromise of sensitivity or count rate capability.

Methods Employed: The design will feature a large number of BGO detectors more tightly packed in a smaller ring than other designs, with electronic advances to shorten the coincidence window to a minimum, thus easing the random coincidence problem which is aggravated by a small ring. A novel detector motion has been developed to further improve resolution.

Major Findings: The detector ring and associated electronics have been designed at NIH and built by contractors. The electronics delivered to date will allow operation with 1 slice; this will be increased to 7 when the system is complete. A computer and display system have been purchased and software is under development here.

The mechanical system for providing the circular translation motion for the detecors has been designed and fabricated by BEIB. The 350 pound detector assembly can be indexed 45 degrees in 0.4 seconds or moved continuously at the required 30 rpm. A truss structure has been completed which supports the detector and tilts its plane of motion at any angle from vertical to horizontal to suit supine or seated patients. A unique spring counter balance mechanism removes the gravitational load from the indexing drive, thereby allowing the use of a small motor which is only required to overcome frictional and inertial forces.

A two channel system for experimental studies was constructed using prototype versions of all critical electronic components, including detector assemblies, preamps, discriminators, and coincidence detectors. The experimental work has verified that the design should meet all program objectives.

Significance: PET imaging with a variety of positron emitting tracers allows many metabolic processes to be studied spatially. The new scanner will increase the spatial resolution which currently limits the potential of the approach.

Publications:

Brooks, R.A., Sank, V.J., DiChiro, G., Friauf, W.S., and Leighton, S.B.: "Design of a High Resolution Positron Emission Tomograph: The Neuro-PET. Journal of Computer Assisted Tomography 4(1): 5-13, February, 1980.

Brooks, R.A., Sank, V.J., Friauf, W.S., Leighton, S.B., Cascio, H.E., and DiChiro, G.: Design Considerations for Positron Emission Tomography. IEEE Transactions Biomed. Eng. Nov., 1980, in press.

Invention Reports: Four have been submitted.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10051-02 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Monolithic Thermopile

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W.S. Friauf	Electrical Engineer	EEES BEIB DRS
OTHER:	C. Mudd	Mechanical Engineer	MES BEIB DRS
	R. Berger	Section Chief	LTD NHLBI

COOPERATING UNITS (if any)

NBS

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.4	PROFESSIONAL: 0.2	OTHER: 0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Process technology developed by the semiconductor industry should be ideal for thermopile fabrication, allowing advances in micro-calorimetry with many applications to biomedical research.

Objectives: Develop a monolithic thermopile for use in micro-calorimeters in place of conventional thermopiles, in order to enhance speed and sensitivity of thermal measurements of reaction kinetics.

Methods Employed: A device has been designed and several batches have been fabricated by NBS on contract. The design is intended to provide good sensitivity with greatly reduced thermal mass and conductivity.

Major Findings and Proposed Course: The first batches of devices work and show considerable promise. However, there have been reliability problems due to the fragility of the devices; hopefully these can be solved by improved mounting techniques. Overall performance is limited by the value of polysilicon sheet resistance obtainable. The performance of random access memories is limited by the same factor, so intensive R and D is being devoted to the problem. It appears that laser annealing may afford a marked improvement and will be investigated.

The present devices, as well as improved ones obtained later, will be incorporated into a micro-calorimeter for more complete evaluation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10053-02 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Membrane Based Sampling Systems for in In Vivo and In Vitro Kinetic Studies

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P.M. Bungay	Chemical Engineer	BEIB DRS
OTHER:	J.P. Froehlich	Senior Investigator	GRC NIA
	R.L. Berger	Section Chief	LTD NHLBI
	J. Fenstermacher	Section Chief	LCHPH DCT
	R.L. Dedrick	Section Chief	ChES BEIB DRS
	P. Krindel	Guest Worker	ChES BEIB DRS

COOPERATING UNITS (if any)

Gerontology Research Center-NIA; Laboratory of Technical Development-NHLBI; Laboratory of Chemical Pharmacology-DCT.

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	1.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Synthetic membranes are being utilized in kinetics studies to provide a means for continuous sampling of the liquid phases from systems in which a dispersed particulate phase is suspended in the liquid phase. In one application sampling equipment is being developed for in vitro study of calcium ion transport and calcium-ATPase activity in suspension of sarcoplasmic reticulum vesicles prepared from homogenates of rabbit muscle. In a second application a study of the mammalian blood-brain-barrier permeability is being aided by the development of an apparatus incorporating a sampler in an arteriovenous ex vivo shunt. In the latter plasmapheresis application pooling the plasma filtrate yields a single sample from which the plasma concentration times time integral can be evaluated for a chemical administered to the animal. Such sampling systems can be useful for the study of the kinetics of other fluid phase systems for which a membrane can be found which is permeable to one chemical of interest but impermeable to another necessary reagent or sink. Thus, other applications might be found in the areas of enzyme kinetics, pharmacokinetics, and the membrane transport of vesicle and cell suspensions.

Objectives: The principal objective is the development of the capability for fluid sampling based upon synthetic membrane technology. In many potential applications sampling by filtration or ultrafiltration may be more appropriate than alternative sampling technique. Ultrafiltration membranes allow the formation of samples representative of the free concentration of small soluble substances. These membranes will retain within the system under study macromolecules and those substances which are bound to them as well as colloidal or cellular components of the system. Other applications may call for the use of larger pore diameter membranes of, for example, macromolecules are to be sampled as well.

Methods Employed: The sampling system generally consists of three elements: (1) a module or modules containing sampling membranes, (2) sample collection equipment, and (3) a means for controlling the rate of production of sample. The membrane module is designed so that the membrane forms a part of the wall of the channel through which the liquid to be sampled flows. Only a small fraction of the liquid is diverted across the membrane to form the sample. The sample is produced as a consequence of a difference in pressure imposed across the membrane. The rate of production of the sample is regulated either by controlling the transmembrane pressure difference or through use of a sample metering pump.

Significance: Membrane sampling is being applied to studies of the transport of calcium ions across sarcoplasmic reticulum (SR). The transport studies are performed in vitro on a suspension of SR vesicles in buffer; the vesicles being created by homogenizing rabbit muscle. The kinetics of calcium uptake by or efflux from the vesicles can be followed by monitoring the appearance or disappearance of calcium from the suspending medium. Also, changes in levels of ATP and inorganic phosphate can be used to infer the kinetics of the calcium dependent membrane ATPase. The membrane in the sampler retains the vesicles (which are thought to be in the range of 0.1-0.5 m in diameter), so that the sample is representative of the suspending media.

A second application concerns in vivo studies of transport across the blood-brain-barrier. The initial objective is the determination of the barrier permeability to selected marker substances. In these experiments a sampler is connected in line with an extracorporeal arteriovenous shunt. By continuously and steadily drawing off a fraction of the shunt flow through the sampler membrane, one can integrate over time the concentration of the marker substances present in the plasma. The value of the integral, together with a determination of the amount of the substance taken up by the brain over the same time interval, permits a determination of the permeability-area transport coefficient. A membrane which retains blood cells is of use in studies in which the transport of the substance into blood cells is sufficiently slow that the cells cannot be considered in equilibrium with the plasma. Use of ultrafiltration membranes may permit determination of the free concentration - time integral, rather than the integral for total plasma concentration, in circumstances of significant binding to plasma proteins.

The in vivo sampling technique can be applied to other acute pharmacokinetic studies for which the plasma concentration-time integral can be of use.

Major Findings: During the current year we conducted a series of experiments to quantify the degree to which the SR vesicles remain intact under the flow conditions to which they will be subjected in the transport studies. We have also conducted studies of the kinetics of calcium binding to SR vesicles. These latter studies have revealed technical problems with the use of the membrane-based samplers which we are presently attempting to overcome.

A premise underlying the concept of filtration sampling is that the marker substance appears in the filtrate (sample) solely because it is carried convectively across the membrane. However, when the plasma concentration of the marker is changing sufficiently rapidly with time, thereby generating spatial gradients in the filtrate tracer concentration, marker diffusion across the membrane and the membrane support can diminish or augment the amount of marker present in the sample. If the filtrate flow rate is sufficiently high or the diffusivity of the marker is small the diffusional contribution should be negligble compared to that from convection. We have been simulating the in vivo animal pharmacokinetic experiments using dye solutions and a sheet membrane module in an in vitro set-up. These simulations are attempting to quantify the conditions under which the sample is representative of the blood plasma kinetics.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 RS 10054-02 BEI

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Biomechanical Study of the Impairment of Wound Healing as a Consequence of a Variety of Cancer Therapies.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. Thibault	Mechanical Engineer	ACES BEIB DRS
OTHER:	T. Talbot	Mechanical Engineer	ACES BEIB DRS
	B. Shamberger	Clinical Associate	SURG. NCI
	M. Brennan	Senior Scientist	SURG. NCI

COOPERATING UNITS (if any)

SURG., NCI

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Applied Clinical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 1.0	PROFESSIONAL: 1.0	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Clinical impression suggests that Adriamycin interferes with wound healing. Biomechanical and biochemical studies of wound healing in the rat have been undertaken. Thus far, we have shown that wound breaking strength is significantly reduced when adriamycin accompanies surgery up to three days post-op. Delaying administration of adriamycin by seven days post-op eliminates the deleterious effect.

It appears that the defect contributing to reduced wound breaking strength in adriamycin treated animals is not due to a collagen maturation defect but is due to a reduction in scar collagen accumulation as measured by "new" hydroxyproline content and reduced fiber diameter as determined by EM measurements.

Previous reports intimated accelerated wound breaking strength by ultrasonic insonation. Four consecutive experiments with insonated and control groups of wounded rats failed to demonstrate this hypothesis.

Objectives: To study effects of a variety of cancer therapy protocols on wound healing, and to attempt to elucidate the underlying mechanism of any such deleterious results.

Methods Employed: Biomechanical studies are both analytical and experimental in nature. Tissue stress-strain relationships are obtained from an Instron tensile testing machine. Biochemical determinations and electron microscopy are performed simultaneously with the biomechanics.

Significance: Results of the study may lead to modified clinical protocols with the intention of promoting wound healing, thereby improving post-operative recovery.

Proposed Course: To study in detail the constitutive behavior of the healing wound.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10055-02 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Breath by Breath Analysis of Computer Controlled Exercise Stress Testing

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. Thibault	Mechanical Engineer	ACES BEIB DRS
OTHER:	W. Schuette	Chief	ACES BEIB DRS
	T. Talbot	Mechanical Engineer	ACES BEIB DRS
	H. Tipton	Mechanical Engineer (Tech.)	ACES BEIB DRS
	R. Winslow	Sr. Scientist	IR-CL-NHLBI

COOPERATING UNITS (if any)

IR-CL-NHLBI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Applied Clinical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.5	PROFESSIONAL: 0.4	OTHER: 0.1

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

In recent years exercise stress testing has become an important diagnostic tool. Most testing of this type is confined to cardiac studies. This system has been developed in order to assess the ability of the subject to transport and exchange oxygen and carbon dioxide between the atmosphere and the cells of the body. A large number of pathophysiologic states limit one's ability to perform these functions efficiently. With this system the anaerobic threshold of the subject during exercise can be detected non-invasively by breath-by-breath respiratory analysis. Oxygen Uptake, Carbon Dioxide Production, Respiratory Minute Volume, Respiration Rate, Heart Rate, and Respiratory Quotion are displayed as a function of Work Rate.

Objectives: To develop a system to analyze the respiratory quotient vs. work rate curve during exercise stress testing in order to determine the anaerobic threshold.

Methods Employed: A Tektronix 4051 programmable calculator and custom designed synchronous integrators and multiplexor has been used to produce breath-by-breath analysis of respiratory quotient as a function of work rate.

Significance: Correlation of the onset of anaerobic metabolism with work level provides a useful clinical measure of the general condition of the hematology patients under study. This method provides a better means of evaluating the efficacy of therapeutic measures.

Proposed Course: To add a pressure transducer to the mouthpiece in order to obtain respiratory power and work.

Publications:

Talbot, T.L., Thibault, L.E., Schuette, W.H., Winslow, R.M., and Tipton, H.W.: Breath-by-breath gas analysis during exercise stress testing. Advances in Bioengineering, 1979.

Schuette, W., Thibault, L., Talbot, T., and Tipton, H.: Synchronous integration - a method for the rapid determination of the mean value of pulsatile physiological signals. Proc. AAMI 15th Annual Meeting, San Francisco, April 13-17, 1980, p. 184.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10057-02 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Development of NMR Imaging Magnet

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S.R. Goldstein	Mechanical Engineer	BEIB DRS
OTHER:	D. Hoult	Electrical Engineer	BEIB DRS

COOPERATING UNITS (if any)

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 1.5	PROFESSIONAL: .7	OTHER: .8

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A novel magnet suitable for nuclear magnetic resonance (NMR) imaging has been designed, and constructed. The magnet employs windings on two hemispherical shells which can be rotated with respect to each other about two orthogonal axes. This arrangement allows prescribed large gradients in magnetic field to be superimposed on an initially homogenous field. The magnet dissipates 7.5 kw of power and has an inner spherical diameter of 0.6 m. Its two power supplies have a short term stability of better than 1 ppm over 10 seconds, and a long term stability of better than 10 ppm. The basic homogeneity of the magnetic field is about 50 ppm over a sphere of diameter 10 cms.

Objectives: To provide a large scale magnet suitable for exploring medical application of NMR imaging. The size of the device will permit examination of babies for detecting fluid filled lesions.

Methods Employed: A magnet consisting of two hemispherical shells each containing two separate windings was constructed. The shells are aluminum castings of 0.67 m diameter with radial flanges projecting out from their surface. Approximately 2 km of 0.37 cm square copper magnet wire was precision wound on each shell between the flanges. The shells can be tilted with respect to each other about two orthogonal axes to produce strong magnetic field gradients. This is accomplished by supporting the hemispherical shells on matching sections of spherical bearings mounted on a pair of support cradles. Leadscrews provide the force needed to tilt the massive device. The magnet dissipates 7.5 kw which is removed by water flowing in copper tubes attached to the inside and outside of the shells.

Design goals are a homogeneity of one part in 10^6 for the axial magnetic field when there is no tilt, and a uniform gradient producing a maximum variation of 1½% of the magnetic field at a 5 cm radius for maximum tilt.

Significance: The above described magnet is one of several essential components of a novel NMR imaging system being developed for a variety of diagnostic applications.

Proposed Course: Test field for homogeneity, uniformity of gradients, long-term stability, and repeatability. Make necessary field corrections required to meet design specifications.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10060-01 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Analytical High Voltage Electron Microscopy and Image Analysis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.D. Leapman	Physicist	BEIB DRS
OTHER:	C.E. Fiori	Physical Scientist	BEIB DRS
	A.F. LeRoy	Chief, Micro. Group	BEIB DRS
	E. Silbergeld	Neurotoxicologist	ETB IRP NINCDS
	J.L. Costa	Staff Physician	CNB NIMH
	K.E. Gorlen	Electronics Engineer	CSL DCRT
	E. Pottala	Electronics Engineer	LAS DCRT
	C.R. Swyt	Physicist	BEIB DRS
	L.K. Barden		CSL DCRT
	J.S. DelPriore		CSL DCRT
	P.S. PLexico		CSL DCRT
	M.A. Douglas		LAS DCRT
	C.C. Gibson	Electronics Engineer	BEIB DRS

COOPERATING UNITS (if any)

Computer Systems Laboratory, DCRT, NIMH, NINCDS

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Microanalysis Group

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 3.0	PROFESSIONAL: 2.5	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The 200 keV Hitachi TEM-STEM electron microscope is now equipped with two microanalytical devices: in electron energy loss spectrometer (EELS) and an energy dispersive X-ray spectrometer (EDX). Both spectrometers have required extensive testing, and significant alterations in the interfacing to the electron-optical column have been necessary. Performance is now substantially improved compared with that after delivery. Such performance will be essential in the biological applications planned in the future. Some preliminary BEIB work has been done on biological and organic samples: the signals or statistics obtained in the spectrum are sufficient for the detection of important elements such as P, N, O and Ca, though the detectability limits have not yet been established precisely. Preliminary data also suggest that energy selective elemental imaging will be achievable using the computer to control the electron probe and to acquire the energy loss signal. Preliminary work has been done with several NIH investigators involving X-ray microanalysis utilizing the improved X-ray performance. Considerably more interaction is planned for the next reporting period.

PHS-6040

Interfacing of the PDP 11-60 computer to the microscope is now approximately 20% complete. Much of the hardware has been constructed, such as the high speed medium accuracy and low speed high accuracy digital to analog and analog to digital I/O channels. Three full-time programmers in the computer sciences laboratory have completed the preliminary structure of the operating system.

Objectives: To provide a capability of performing elemental microanalysis on Electron Microscope samples utilizing an Electron Energy Loss spectrometer and a non-dispersive X-ray detector.

Methods Employed: A 200 keV Transmission Electron Microscope with scanning transmission capability is utilized to photoionize microvolumes (containing as small as 10^{-20} grams of matter) of electron microscope specimens. By performing electron spectroscopy on the transmitted electrons and X-ray spectroscopy on the X-rays coming from the photoionized volume of the specimen it is possible to perform elemental microanalysis.

Significance: Electron beam microanalysis permits the solution of certain biological problems which would be difficult, or impossible, by other means.

Proposed Course: To study in detail the problems of applying the technique to biological research and to study in detail the problems involved in this application.

Publications:

Leapman, R.D.: "Extended core edge fine structure in the electron microscope." Proceedings of the 38th Annual Meeting of EMSA, Reno (1980). Baton Rouge, G.W. Bailey (Ed.).

Fiori, C.E., Leapman, R.D., and Gibson, C.C.: "Electrostatic deflection system for use with an electron energy loss spectrometer." Proceedings of the 1980 Meeting of the Microbeam Analysis Society.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10061-01 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Automated Scanning Electron Beam X-ray Microanalysis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C.E. Fiori	Physical Scientist	BEIB DRS
OTHER:	A. LeRoy	Chief, Micro. Group	BEIB DRS
	K.E. Gorlen	Electronics Engineer	DCRT
	E. Pottala	Electronics Engineer	DCRT
	D.L. Fry		LEA NHLBI
	C.R. Swyt	Physicist	BEIB DRS

COOPERATING UNITS (if any)

CSL, LAS, DCRT; and LEA, NHLBI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Microanalysis Group

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 2.0	PROFESSIONAL: 1.5	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐X(c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The principal instrumentation for this project, a Cameca MBX 2-50 keV scanning electron beam microprobe, was delivered in January, 1980, and installed during February and March, 1980. The initial performance testing has been accomplished and the machine has been accepted. Some preliminary collaborative biological work is being done and more is planned after modifications are completed to permit the automatic displacement of the sample under the electron beam. More complete automation of the microprobe is being planned and most of the necessary hardware has been ordered. The microprobe will be interfaced to a PDP 11-60 computer. The automation will permit computer control of the specimen stage, electron beam scanning and wavelength dispersive X-ray spectrometers. The bulk of the software will start to be written towards the end of the next reporting period and will require approximately one year to complete.

Objectives: To provide a capability of performing elemental microanalysis on both bulk and thin biological specimens utilizing focussed electron beam induced X-ray spectroscopy.

Methods Employed: A focussed 2-50 keV electron beam is utilized to photoionize microvolumes (containing as small as 10^{-18} grams of matter) of biological specimens. By performing X-ray spectroscopy utilizing Bragg angle X-ray spectrometers, on the X-rays leaving the photoionized volume of the specimen it is possible to perform elemental microanalysis.

Significance: Electron beam microanalysis permits the solution of certain biological problems which would be difficult, or impossible, by other means.

Proposed Course: To apply the technique to biological research and to study in detail the problems involved in this application.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10062-01 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

IEEE-488 General Purpose Interface Bus Program Development

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	T.R. Clem	Electronic Engineer	EEES BEIB DRS

COOPERATING UNITS (if any)

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.3	PROFESSIONAL: 0.2	OTHER: 0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The ability to produce instrumentation systems using several individual instruments interconnected via the IEEE-488 General Purpose Interface Bus (GPIB) is being developed. With the cooperation of the BEIB-SERP a variety of bus-compatible instruments is being acquired to complement this ability.

Objectives: Develop expertise in the Branch in the use of IEEE-488 GPIB-compatible instruments and controllers. Recommend types of bus-compatible instruments for acquisition by the BEIB-SERP.

Methods Employed: Prototype systems are assembled from equipment available in the rental program and simulation tests run. A system was assembled and set-up in the laboratory of Dr. John Pisano, HE, NHLBI, which digitized and stored the solvent baseline from his liquid chromatograph. This stored baseline was subtracted from the LC output each time a sample was run. The availability of the bus-compatible instruments and controller allowed the quick delivery of a system to confirm the feasibility of the technique and allowed the investigator to be able to take advantage of the data improvement while a dedicated unit was being designed and fabricated.

Significance: The capability of assembling an instrumentation system with a controller and GPIB-controlled instruments allows the EEES to provide a rapid response to an investigators call for instrumentation. By assembling a system with "off-the-shelf" instruments from the SERP, the cost of a special-purpose measurement or control system can be kept quite low. If the experiment is a short-term project the instruments can be returned to the SERP with virtually no expenditures, by the investigator, for equipment.

Proposed Course: Maintain state-of-the-art capability in the field of bus-compatible instruments and controllers. Seek to make this capability better known and understood around NIH.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10063-01 BEI

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Digital Thermistor Thermometer

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	T.R. Clem	Electronics Engineer	EEES BEIB DRS
OTHER:	R. Berger	Section Chief	LTD NHLBI

COOPERATING UNITS (if any)

LTD, NHLBI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.2	PROFESSIONAL: 0.1	OTHER: 0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

High resolution and high accuracy thermistor thermometers, using microprocessors as control components, are being developed. These units are suitable for process control and data logging uses in the laboratory.

Z01 RS 10063-01 BEI

Objectives: Design and construct a series of high resolution, high accuracy (better than ± 0.01 °C) thermometers using precision thermistors as sensing elements and digitizing the results for process control and/or data logging.

Methods Employed: The thermometers are each designed around a microprocessor and high resolution digital-to-analog and analog-to-digital convertors. A known excitation current is applied to the thermistor and the resultant voltage is read. The power level to the thermistor is controlled at a constant value for a minimum of self-heating error. The resistance of the thermistor is calculated and the corresponding temperature is derived from a look-up table which is generated for each thermistor individually.

Significance: These instruments provide high accuracy laboratory thermometers for precision temperature measurements.

Proposed Course: Design additional thermometers with emphasis on different features, i.e., speed, compactness, etc.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10064-01 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Indirect Blood Pressure Measurements in Laboratory Animals Using Oscillometry

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E.C. Walker	Mechanical Engineer	BEIB DRS
	J.E. Pierce	Chief, LAMSS, OD	NHLBI

COOPERATING UNITS (if any)

NHLBI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering and Applied Clinical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	1.0	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Currently there are no reliable indirect methods of measuring blood pressure in dogs. Traditional techniques, used in humans, are unsatisfactory primarily because they require the placement of a transducer over the artery being monitored.

Because of the unreliability of traditional techniques we have been investigating a technique called oscillometry. Oscillometry is a method of measuring blood pressure by analyzing the pulse pattern of the cuff pressure oscillations.

In practice, a cuff is placed around a limb and inflated to a pressure above systolic and then slowly deflated. While the cuff is being deflated the amplitude of oscillation in cuff pressure, produced by the arterial pulse beneath the cuff, is monitored. Systolic pressure is indicated by the first significant increase in oscillation amplitude. Diastolic pressure is indicated as the lowest cuff pressure at the point of maximum oscillation in cuff pressure. Currently most investigators using this technique take the point of maximum oscillation to indicate mean arterial pressure.

Objectives: The primary objective of this project is to develop an instrument to indirectly measure peripheral arterial blood pressure in laboratory animals.

Methods Employed: Anesthetized and awake studies were performed on laboratory dogs and pigs. Simultaneous direct arterial and indirect oscillometric cuff pressure measurements were obtained. A laboratory simulation of the oscillatory mechanism has also been employed.

Significance: Animal surgery labs and other laboratories or veterinarian offices could use an indirect device on a daily basis. For various laboratory studies monitoring blood pressure in awake animals is very desirable, particularly with protocols involving atherogenic diets, and drug therapy. Another area of application would be in screening animals for hypertension research. For surgical procedures, an indirect technique will allow blood pressure monitoring before and during induction of anesthesia.

Major Findings: The results of 19 dog experiments and many laboratory simulations indicate that oscillometry measures systolic and diastolic pressures but not the mean arterial pressure (contrary to previous interprelations of the measurement). Future efforts will be directed toward designing an automated oscillometric instrument.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10065-01 BEI

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Transient Response of Micro-Calorimeters Using R-C Analysis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C.P. Mudd	Biomedical Engineer	BEIB, DRS
OTHER:	R.L. Berger	Section Chief	LTD, NHLBI

COOPERATING UNITS (if any)

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Mechanical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1	1	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The behavior of current microcalorimeters lies between that of true adiabatic or bomb calorimeters and isothermal calorimeters. The location between these extremes depends upon a compromise involving many criteria but most importantly, time constant and sensitivity. The use of an R-C model of the system and Laplace transform techniques will allow us to study the transient behavior of the system to a variety of inputs.

Objective: The objective of the analysis is to determine the input when given the output of the system. Since a micro-calorimeter functionally integrates the signal, the reverse will require, in essence, differentiation and thus will enhance the system noise. Although there are four approaches to this problem that have shown limited success, the FEST (Finite Element Simulation Technique) has yielded the best results to date.

The International Calorimetry Conference has devised a sequence of 7 heat pulses of varying amplitudes and duration to simulate the range of reactions to be encountered in practice. These pulses, termed the Warsaw-Cadarache Pulses, are the input to the model.

Significance: A model has been developed in which the physical system is divided into separate components each of which has a thermal R and C value associated with it. Based on the geometry, these can be determined quite accurately. Thus, the transfer function of each component can be found and when combined will yield the transfer function of the entire system. The results have already been used to redesign the input stage of the calorimeter to reduce loading (thermally), thus resulting in faster rise times or higher a-c sensitivity. The model predictions using the Warsaw-Cadarache Pulses are in the process of being compared to FEST computer results.

Proposed Course: If the results of the comparison with FEST are favorable, this approach will have three advantages: (1) It relies heavily on a known technique for which the mathematics is well documented and relatively simple; (2) it allows the user to evaluate design changes on paper to optimize performance for a given set of operating conditions; and (3) it is (as far as calorimetrists are concerned) inherently less abstract and is an analog of the physical system.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10066-01 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Egyptian Training Project

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C.P. Mudd	Biomedical Engineer	BEIB DRS
OTHER:	H.W. Metz	Chief	RIS BEIB DRS

COOPERATING UNITS (if any)

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering and Research Instrumentation

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 1	PROFESSIONAL: 1	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The development of criteria and mechanisms for evaluation of prospective Egyptian engineers for possible training at NIH (RIS) in equipment repair. The final goal is the establishment of repair centers in Egypt for scientific and medical equipment.

Objective: The ultimate objective is the establishment of successful repair centers in Egypt. This will depend upon 3 factors: (1) selection of appropriate repair personnel; (2) proper training of the personnel; and (3) adequate hardware (stock parts, test equipment, etc.). The immediate objective of this project is area 1 and to some extent area 2. We cannot rely on the internal (Egyptian) selection mechanisms because they emphasize too heavily academic or scholastic achievements with very little regard to practical experience or applications.

Significance: A course was developed consisting of 4 weeks of matching lectures and labs. The material was selected to be more advanced than that in two preceding courses (NRC I and NRC II) presented by USAID. This new course had two primary goals: (1) to evaluate candidates for possible future training at NIH and (2) to provide a practically oriented, more advanced course to follow NRC I and II.

To achieve these goals, the course was divided into two parts. The first covered the use of linear and non-linear integrated circuits while the second covered their application involving transducers.

In the first part, the emphasis was on the practical limitations of integrated circuits. This was intended to bring all of the students up to an equal level to allow a more meaningful aptitude evaluation in the second part.

The second part involved using the basic circuits of part one to form signal processing blocks to convert transducer signals into useable and appropriate outputs. Here, the emphasis was on practical design which involves making intelligent compromises concerning signal to noise ratio, bandwidth, gain, etc.

Proposed Course: The course is tentatively planned for presentation November-December 1980. Previous versions were presented in the Summers of 1978 and 1979.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10067-01 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Review and Integration of Micro-Calorimeter System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C.P. Mudd	Biomedical Engineer	MES BEIB DRS
OTHER:	R.L. Berger	Section Chief	LTD NHLBI
	W.S. Friauf	Electrical Engineer	EEES BEIB DRS
	C. Gibson	Electrical Engineer	EEES BEIB DRS

COOPERATING UNITS (if any)

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering and Electrical and Electronics Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 1	PROFESSIONAL: 1	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

For the past several years, considerable time and effort have been expended on the various aspects of a micro-calorimetry system. Due to the complexity and interdisciplinary nature of the work, the first model did not perform to expectations. Several problem areas were identified and led to subsequent projects (e.g. 71-78-167E, Monolithic Thermopile Design and 71-80-144M, R-C Analysis of Micro-Calorimetric Transient Response). The review and redesign led to the achievement of heat resolution of 300n watts and long-term stability of ± 200nw (rms). A list of performance criteria for a differential calorimeter has been developed and the new sensor design is being evaluated in a new calorimeter.

Objective: The objective for the microcalorimeter is to reduce all noise contributions to approximately the same magnitude. In this case, the ultimate limitation on resolution and drift is determined by the electronics (300n watts and ± 200n watts (rms)/24 hours respectively in terms of the measurement). The low long-term stability is desirable for proposed metabolic studies involving cancer cells and the high resolution is desirable for adequately determining enzyme kinetics.

Significance: To date, we have produced one differential batch micro-calorimeter which meets the above specifications. To achieve this, we identified and eliminated the following problems:

(1) A "motion artifact" which occurred when the rotor was inverted to mix the reagents. The cause was two-fold: bearing heat from mis-aligned bearing supporting the rotor and mixing of air within the constant temperature chamber which in effect produced an impulse response from the temperature control circuit. To reduce the temperature gradient within the chamber, special heaters were designed to give a uniform heating density ($watts/cm^2$) over the surface.

(2) A drift linked to room temperature was identified and reduced by adding a second control on the outside of the calorimeter to hold the temperature constant ± 0.2°F.

(3) New sensors were purchased which increased the sensitivity by a factor of 3. From a model of the system, we were able to redesign the input stage (mechanical) so that the rise time remained unchanged.

Proposed Course: We are currently in the process of building a complete calorimeter system for an investigator at NIH. The system will be built by a private contractor and we will evaluate its performance after construction.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10068-01 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Rat Vocalization Analysis System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	James L. Hill	Visiting Associate	LBEB NIMH
OTHER:	John B. Calhoun	Research Psychologist	LBEB NIMH
	W.J. Vaughn	System Programmer	STD NIMH
	Horace E. Cascio	Electronics Engineer	BEIB DRS

COOPERATING UNITS (if any)

Laboratory of Brain Evolution and Behavior

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.9	PROFESSIONAL: 0.8	OTHER: 0.4

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Vocal communication among members of free ranging population of rats housed in a complex laboratory. Enclosures are either audible or are ultrasonic. Ultrasonic vocalizations tend to be more prolonged and to form patterned sequences. Rats vocalizing simultaneously are capable of utilizing separate frequency bands so that each vocalization signal can be distinguished. Rats required to perform cooperatively appear to exhibit different and, possibly more complex vocalization patterns, than those rats with free access to food and water resources.

Objectives: To design and install a system to investigate whether the quality, quantity and pattern of rat vocalization change when the animals are required to perform complex cooperative behaviors to meet their physiological needs.

Methods Employed: A recording system was designed using a special microphone and amplifier which has a frequency range (20 Hz - 200 KHz) to pick up the audible and ultrasonic vocalizations. The microphone was mounted in a parabolic reflector to increase directivity. The vocalization signal is coupled to a Tektronic 5L4N Spectrum Analyzer and the video output of the 5L4N is applied to a PDP11/04 computer. Electronic interfacing circuitry was required for the video signal and also to provide a start pulse to synchronise the 5L4N to the computer. Software within the computer then classified the vocalizations according to type and frequency. Graphics output is of two major types: (1) the trace of the power curve and (2) a representation of each vocalization as a vertical line spanning the frequency band. To aid in the determination of the type of vocalizations that are associated with specific behaviors, an intercom system was installed so that a direct observation could be made with the computer recording. This vocal-ethogram will provide the base line for comparison of experimentally induced changes in vocalization on behavior.

Major Findings: Most of the sounds are ultrasonic vocalizations. Sounds were distinguishable as to squeaks, when rats move through the environment and to conversations between rats. At present the investigation is continuing to correlate the occurrence of these and other patterns of vocalizations with visual observations of social behavior and computer records of movement patterns.

Proposed Course: To provide additional instrumentation as required to study the comparison of the vocalizations of rats required to perform cooperative behaviors with those of rats that can satisfy their needs *ad lib*, and to add a comparison of the vocalizations of neopalliectomized rats to those of normal rats to determine the contribution of the neocortex to the regulation of the type and patterning of vocalizations.

Significance: Vocal communication, which plays a major role in mammalian social behavior, may become changed as an outward manifestation of stress or some altered brain function. An animal model, is being presented, that is being used (1) to discover how long-term stress influences vocal communication and (2) to investigate the role of the neocortex in the regulation of vocal communication. Furthermore, the extremely complex and prolonged patterns of vocal communications between rats suggest that Norway rats, *Rattus norwegicus*, may lead to the use of this species as an animal model for the study of the early evolution of communication that culminated in human language.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10069-01 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Two Automated Test Sets Mod. III for Checking Safety of Biomedical Equipment

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C. Wooten	Electronics Engineer	EEES BEIB DRS
OTHER:	H. Cascio	Electronics Engineer	EEES BEIB DRS
	W. Friauf	Section Chief	EEES BEIB DRS
	R. Corsey	Electronics Engineer	ACES BEIB DRS

COOPERATING UNITS (if any)

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronics Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 1	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

These safety test units are designed to provide accurate measurements of the ground resistance and current leakage of equipment located in the Clinical Center. Two test sets have already been in operation for 7 years. These new units will perform the same tests, but they have been updated to provide automated data acquisition and storage.

Objectives: The objective is to provide an automated test set which can safely and accurately measure the parameters of devices in their operating environment. Also, the objective is to facilitate the handling and storage of this data, so that the safety of the equipment being tested can be better evaluated and statistical and trend analysis of past and present data can be done.

Methods Employed: Using microprocessor technology, manual input and bar code scanner input can be interfaced to the test set to provide identification of the equipment and annotations on the test itself. The data is output to cassette tapes which are compatible with the IBM/360 or DEC 10 computer. A program is being written to input the data and file it for better documentation and analysis for the user.

Significance: By monitoring the results from the safety test data, problems in the safety and every day operation of the equipment can be detected or even predicted to prevent hazards to the patients.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10070-01 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Conceptual Adaptation and Evolution

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.B. Calhoun	Research Psychologist	LBEB NIMH
OTHER:	R.W. Ridez	Research Psychologist	LBEB NIMH
	G.A. Bagley	Computer Programmer	LBEB NIMH
	H.E. Cascio	Electronics Engineer	BEIB DRS
	A.H. Rich	Mechanical Engineer	BEIB DRS
	D.R. Ahuja	Research Fellow	SPH HU
	R.A. Newell	Electronic Engineer	STD NIMH

COOPERATING UNITS (if any)

Laboratory of Brain Evolution and Behavior

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronics Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 3.4	PROFESSIONAL: 1.2	OTHER: 2.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Hybrid rats, Rattus norwegicus, are used to investigate a model of nongenetic adaptation with rats living in a stable environment under crowded conditions. A control population received food and water under normal conditions with no demands for learning cooperative tasks placed upon them. Rats maintained at twice normal population density obtained food and water resources by learning cooperative tasks. Results indicate that these latter rats show: (1) reduced intensity of fighting, (2) increasing maintenance of body weight, and (3) development of modes of reproductive control, including killing of young. We conclude that acquisition of cooperative behavior reduces crowding related stress.

Objectives: To design and fabricate testing apparatus to enable the determination of the effects of an investigator-induced acquisition of cooperative behaviors by rats living at twice optimum density in contrast to a control population without the opportunity to acquire cooperative behaviors.

Methods Employed: A controlled drinking device was fabricated that can be switched to a cooperative drinking mode which required that one rat must be present in each of two adjacent units for either one to obtain water. In addition to their normal sources of food and water, three different reward situations were provided, each with a different reward. First, a drinking device which gives saccharine water; secondly, a sunflower seed dispenser, and thirdly, a swing rod which has an orange quarter placed at the bottom of the rod. The above apparatuses can be altered after a period of time to deman cooperative behavior in order to obtain rewards. A computer data acquisition system continuously monitors movements between habitat compartments and response to food and water acquisition apparatuses by identity of each rat.

Major Findings: The COOP experimental subjects, in contrast to the DISOP controls, exhibit: (1) less intense fighting with fewer wounds received, (2) sustained greater body weight, (3) decreased conception, and (4) increased killing of recently weaned young by adult females. These results acquire meaning when viewed against a finding of a difference in the distribution of "social power," the ability to engage in, and to exercise dominance during social encounters.

Proposed Course: Continue to provide technical support to this project until its conclusion.

Significance: Humans are exposed to environments which are increasingly becoming more variable, complex, and changing. The current rate of change introduces undesirable stress on individuals and produces broader instabilities in society. The research with rats suggest more cooperative social roles can ameliorate stressful consequences of physical and social environmental change. However, introduction of cooperative social roles produce instabilities in social relationships which last longer than does the learning of the new cooperative manners of behaving.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10071-01 BEI

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Fiber Optic Probes for Cardiac Instrumentation

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S.R. Goldstein	Chief	MES BEIB DRS
OTHER:	R. Patterson	Senior Investigator	NHLBI
	J.I. Peterson	Chemist	ChES BEIB DRS

COOPERATING UNITS (if any)

Cardiology Branch, NHLBI

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Mechanical and Chemical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 1.0	PROFESSIONAL: .8	OTHER: .2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The use of miniature fiber optic probes for acute insertion into canine myocardium is being investigated. Measurements of pH, local blood flow and local capillary permeability in the presence of various interventions is contemplated. Practical problems dealing with insertion into tissue, validation of readings, elimination of motion artefacts, and overall characterization of in-vivo performance are of major interest. Preliminary results are encouraging.

Objectives: Perfect and enhance previously developed techniques (described in last years report) utilizing miniature fiber optic probes to measure pH, tissue perfusion and capillary permeability in canine hearts in vivo.

Methods Employed: Utilize existing miniature fiber optic probes to perform measurements in acute dog experiments. Perform tests to determine practical problems, e.g., breakage, tissue insertion, artefacts, calibration difficulties, elimination of motion artefacts, zero shifts, hysteresis, etc. Develop solutions to above problems using improved probes and signal processing instrumentation.

Significance: At present there are no completely satisfactory techniques for measuring local pH, perfusion, and capillary permeability in-vivo in an "on-line" manner. Perfection of these measurements would represent a great advance in the techniques presently available to experimental cardiologists and other biomedical researchers not only in terms of convenience, but also in terms of opening up many new areas of investigation.

Major Findings and Proposed Course: On the basis of preliminary experiments it appears that:

(a) pH measurements behave in a qualitatively correct manner but difficulties still remain with inserting the 0.3 mm diameter probe without traumatizing the local region when using in the beating heart; validation of probe accuracy must be performed. A second generation multi-channel input interfaced with a Tektronix 4052 calculator will be built.

(b) Perfusion measurements are feasible, i.e., there is acceptable signal-to-noise ratio. Motion artefacts must be eliminated and an approach is being investigated. Validation using microspheres will be performed once an automatic gain ranging system is implemented so that traces can be reliably obtained. Various flow limited fluorescent markers in addition to fluorescein will be sought.

(c) Capillary permeability studies will be investigated after the perfusion and pH techniques have been perfected. Fluorescent labeled compounds of appropriate molecular weight (possibly fluorescein labeled albumin) will be sought and used.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 10072-01 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Clinical Evaluation of Membrane Oxygen Dissociation Curve Analyser

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W.H. Schuette	Chief	ACES BEIB DRS
OTHER:	L. Thibault	Mechanical Engineer	ACES BEIB DRS
	H. Tipton	Mechanical Engineer	ACES BEIB DRS
	D. Lees	Staff Anesthesia	CC NIH

COOPERATING UNITS (if any)

CC - NIH

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Applied Clinical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2	1.5	.5

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A fully automated, computer controlled method for determining and plotting the entire hemoglobin-oxygen dissociation curve on less than .5 cc of blood has been developed and is being introduced to clinical practice. A micro-computer controls the calibration of the system as well as the initial desaturation and subsequent saturation of the blood specimen.

Methods Employed: Initially the specimen is desaturated by exposure to a CO_2/N_2 mixture. Once the pO_2 falls below 0.5 torr, the computer automatically starts the saturation with a mixture of oxygen and CO_2. Gas is exchanged with the sample in a reaction cell across a silicone rubber membrane which mechanically separates the two phases. The sample solution is contained within an annular region formed by the cylindrical membrane and the sample cavity walls where it is stirred by a thin-walled cupshaped stirrer, magnetically coupled to an outside motor-driven rotor. A conventional polarographic oxygen electrode continuously monitors the partial pressure of oxygen in the sample. The amount of oxygen delivered to the sample is calculated by integrating the diffusion equation and the measured pO_2 gradient across the thin silicone membrane.

Major Findings: The described system appears to be a simple and reliable way of obtaining the hemoglobin-oxygen dissociation curve for clinical applications.

Publications:

Thibault, L.E., Kusnetz, R., Winslow, R.M. and Berger, R.L.: An instrument to determine the hemoglobin-oxygen equilibrium curve based on an analytical model for the transport of oxygen across a semi-permeable membrane. Advances in Bioengineering, American Society of Mechanical Engineers, New York, 1978, pp. 107-108.

Thibault, L.E., Schuette, W.H., and Lees, D.E.: An instrument to determine the hemoglobin-oxygen equilibrium curve based on the calculated diffusion of oxygen across a semi-permeable membrane. Medical and Biological Engineering and Computing Journal of the International Federation for Medical and Biological Engineering (In press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10073-01 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Secondary Emission Experimental Mass Spectrometer

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. Kelner	Visiting Associate	BEIB DRS

COOPERATING UNITS (if any)

LAB/BRANCH Biomedical Engineering and Instrumentation

SECTION Microanalysis Group

INSTITUTE AND LOCATION DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.3	PROFESSIONAL: 0.3	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The principal instrumentation for this project, the SIMS-quadrupole mass spectrometer, PE-270 double-focusing mass spectrometer, electron and ion guns will not be delivered until the next reporting period. The major effort on this project to date has been in the evaluation of the literature on the related subjects to the proposed instrument: secondary ion mass spectrometry, surface ionization, secondary ion and electron emission, cold emitters; establishment of specifications of the instrument. The SIMS mass spectrometer chosen is an Extranuclear "plus" SIMS secondary ion mass spectrometer, the double-focusing mass spectrometer model PE-270 to be transferred to NIH from the Argonne Res. Labs, electron gun EFG-7J and power supply EGPS-7J will be purchased from Kimball Physics Inc.; the ionization chamber has been ordered from MDC Manufacturing Co., and will consist of a stainless steel beel-jar with four 6" and four 2.75" CF flanges and two 8" flanges; the vacuum system Balzers TSH-511 will be incorporated to evacuate the ionization chamber.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10074-01 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Study of analytical applications of QUISTOR

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. Kelner	Visiting Associate	BEIB DRS
OTHER:	S. Markey	Chemist	LCS NIMH

COOPERATING UNITS (if any)

LCS NIMH

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Microanalysis Group

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 1.0	PROFESSIONAL: 1.0	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The quadrupole ion store (QUISTOR) or three dimensional ion trap has received little attention among analytical chemists compared to the quadrupole mass filter or two dimensional quadrupole. This is in part due to the fact that QUISTOR primarily has been developed, studied, and used by physicists as partial and total pressure analysers and residual gas analysers and most recently as electronically controlled ion-molecule reaction chambers. Recent works by G. Lawson, R.F. Bonner and R. March employing a three dimensional quadrupole ion trap as an ion source for a mass spectrometer has opened new avenues for the QUISTOR as an analytical tool. The QUISTOR is expected to be more compact, the resolution of the instrument would not be mass dependent as for quadrupoles, and the sensitivity of the device, specifically when detecting single ions, may be improved compared to a quadrupole mass spectrometer combined with a conventional ion source.

The Quadrupole Ion Store was constructed and machined from stainless steel, specifications for the driving electronics have been established, RF-generator modified by Exranuclear Labs. will be used to power the QUISTOR, pulse electronics will consist of a Boxcar Averager and Gated Integrater by EG&G, two pulse generators by HP, X-Y Recorder and Tektronix Oscilloscope.

Objectives: To develop a QUISTOR-mass spectrometer combination and to study the possible applications in analytical mass spectrometry.

Methods Employed: A three dimensional quadrupole electric field will be used to store ions of interest. This field will be formed by three electrodes of a hyperbolic geometry made of stainless steel, which will consist of two "endcaps" and one central ring. The electron gun will be used to ionize molecules of compounds to be studied. The RF-electric field will be applied to a ring electrode and creation and ejection pulses to the end-caps.

Significance: Development of a three-dimensional ion store and its application in mass spectrometry may result in improvements of detection capabilities of existent instruments and may increase limits of detection of compounds of biological interest.

Proposed Course: Construct the driving electronics and detection system for the QUISTOR. Test the device and study its storage capabilities. Interface the quadrupole ion trap with the gas inlet sysem and the gas chromatograph. Employ different types of electron emitters: hot filaments, field emitters, cold cathodes and find the most suitable emitter for the proposed device. Study the applicability of the QUISTOR to mass spectrometric analysis of drugs and other compounds of biological interest.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10075-01 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Development of a new method for resolving power measurement

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. Kelner	Visiting Associate	BEIB DRS
OTHER:	D. Rosenthal	Senior Chemist	CLSG RTI

COOPERATING UNITS (if any)

Chemistry and Life Sciences Group, Research Triangle Institute

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Microanalysis Group

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 1.0	PROFESSIONAL: 1.0	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Decachlorobiphenyl and decabromobiphenyl have been analyzed under positive and negative ion chemical ionization and positive ion electron impact conditions for the purpose of using these compounds as references to evaluate the resolving power of mass spectrometers in a wide mass range (M/Z 100-1000). Molecular clusters and some fragments have been detected with different types of mass spectrometers: magnetic sector as well as quadrupoles, including A.E.I. MS-9, LKB-9000, LKB-2091, Finnigan 3200 and Finnigan 4000. The criteria to determine the resolving power have been found based on the measurement of the minima of two adjacent peaks of the molecular cluster of DCB or DBB. Molecular clusters for DCB and DBB were determined theoretically by plotting the individual ions which constitute each profile at the desired resolution using a standard Gaussian distribution of intensities, and then summing the individual ions with the weighting factors derived from the theoretical statistical isotope distribution ratios of carbon, chlorine, and bromine. By comparing the theoretical values of minima vs. resolution with the experimentally found values of minima between the same two adjacent peaks, the resolving power of a given mass spectrometer can be determined. The method

developed here and the reference compounds DCB and DBB will be recommended to manufacturers and users of mass spectrometers as an easy and accurate way to estimate the resolving power of their instruments both for instrument acceptance and as a routine check-out.

Objectives: To develop a method to measure the resolving power of various types of low resolution mass spectrometers which will be easier, faster and require less effort than the conventional methods.

Methods Employed: Theoretical values of ion abundances for molecular clusters of decachlorobiphenyl and decabromobiphenyl will be used to determine the resolving power of mass spectrometers by comparing them with the experimental values of minima between two adjacent peaks in the molecular cluster.

Major Findings: The calibration curves MIN=f(R) have been found for molecular clusters of DCB(M/Z 498) and DBB(M/Z 944). The comparison between the theoretically derived MIN values and the experimental data show good agreement between observed and calculated values in the resolution range of 150-500 for DCB and 300-900 for DBB. Thus the two compounds cover the useful range of a low resolution mass spectrometer, i.e., 150-900. It also has been found that DBB may be used as a sensitivity test reference for quadrupole mass spectrometers in a high mass range (600-1000). It can be done by comparing intensities of the peaks centered at M/Z 944 and M/Z 784. Their ratio should be about 0.5.

Significance: A simple method to determine the resolving power of mass spectrometers has been developed. The method can be used in all types of mass spectrometers and with different ionization techniques (electron impact, chemical ionization, positive or negative ions, etc.). The method will be beneficialy to all mass spectrometry users and may improve the specifications of the instruments at their acceptance.

Proposed Course: The experimental data for the measurement of the resolving power on different types of mass spectrometers will be analyzed. The inlet system to conveniently introduce DCB and DBB into the ion source region of the mass spectrometers will be developed. The possible automation of the procedure with the help of a dedicated computer system (MS/DS) will be evaluated.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 10076-01 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Elemental Analysis of Microdroplets

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	A.F. LeRoy	Chief, Micro. Group	BEIB DRS
OTHER:	N. Roinel	Chemist	CEN, France

COOPERATING UNITS (if any)

Department of Biology, Centre d"Etudes Nucleaires, Saclay, France

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Microanalysis Group

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 1.5	PROFESSIONAL: 1.5	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES [✓ ☐ (c) NEITHER]

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The principal instruments used in this project are the Cameca MBX 2-50 KeV scanning electron beam microprobe and a Cameca MS-46 electron microprobe, each equipped with two wavelength dispersive spectrometers. Quantitative elemental analysis in volumes of the order of 10^{-10} liter are possible using these instruments. The signal for some elements changes with time as a function of beam current density, sample mass thickness and some other characteristics of the samples. A systematic quantitative study of the variables that affect stability of the signal has been undertaken to establish the ranges of values of these variables that permit usable results to be obtained.

Z01 RS 10076-01 BEI

Objectives: To establish the ranges of instrument operating conditions that yield stable signals for the elements analyzed with the MBX microprobe.

Methods Employed: Mathematical analysis of data obtained on representative microdroplets to quantify dependence of element X-ray signal on operating conditions as a function of time.

Significance: To provide a sound basis for quantitative analysis of microdroplets.

Proposed Course: To extend the number of variables included in the study to include temperature of the sample analyzed and the sizes of crystals analyzed.

Publications:

Roinel, N.G. and LeRoy, A.F.: Variations in characteristic signals of the elements during microprobe analysis of droplets: A review. Microbeam Analysis, 129-132, 1980.

LeRoy, Andre and Roinel, Nicole: Quantitative analysis of lyophilized solutions: Loss of elements during the irradiation time as a function of sample current density and mass thickness. Proceedings of the Seventh European Congress on Electron Microscopy, The Hague, The Netherlands, August, 1980.

VRB Special Project Reports

1979-80 DRS ANNUAL REPORT

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00001-10 VR

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)
Animal Model Development

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C.T. Hansen	Geneticist	VRB	DRS

COOPERATING UNITS (if any)
None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Small Animal Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	0

CHECK APPROPRIATE BOX(ES)
☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The program is designed to meet future requirements for biological test systems used in biomedical research. Since its inception in the early 1970's, some 75 new model systems have been developed utilizing the internal resources of the National Institutes of Health Genetics Resource (NIHGR). These include model systems for immunology, infectious diseases, parasitology, cancer, immune comples diseases, behavior, alcoholism, metabolic diseases to include diabetes mellitus, and cardiovascular diseases to include hypertension. The majority of the projects are collaborative in that they involve a close working relationship with the clinical investigator.

PHS-6040
(Rev. 10-76)

Objectives: A limiting factor in understanding cause and effect relationships in life and disease processes is often the availability of the appropriate test system. The goal for this project is to develop these test systems which are designed to meet the requirements for a broad spectrum of clinical diseases.

Methods Employed: The basic requirement for undertaking these projects is that the characteristic of interest has a substantial genetic component in order that appropriate breeding procedures may be utilized.

Major Findings: One of the model systems discussed appears to have considerable potential for the study of the immunology of infectious diseases as weel as parasitology. Also, this model has promise for cancer research since its response to xenografting human neoplasms is far superior to previously used models.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00002-09 VR

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Development of Diets for Laboratory Animals

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.J. Knapka	Nutritionist	VRB	DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH

Veterinary Resources Branch

SECTION

Small Animal Section

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	0.5	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A continuing program in laboratory animal nutrition involves various stocks and strains of guinea pigs, rats, and mice maintained in conventional and specific pathogen-free environments. This program utilizes a series of factorial designed feeding trials to evaluate the effect of either varying nutrient concentrations or different dietary ingredients on growth, reproduction, and maintenance of the various species. The objective of this program is to develop open formula natural ingredient diets for these species so the nutritional status of production and research animal colonies can be improved. Data generated by this program are used as a basis for estimating the nutrient requirements of the species involved and also for ascertaining differences in nutrient requirements for stocks or strains within a species.

PHS-6040
(Rev. 10-76)

Objectives: To improve the status of NIH production and research colonies of laboratory animals by identifying the quantitative nutrient requirements of specific species and providing open formula diets containing the required nutrient concentrations. To identify potential differences in nutrient requirements among stocks and strains of small laboratory animals and during the various phases of their life cycle--growth, reproduction, and maintenance. To provide NIH ivestigators with modifications of open formula diets to accommodate specifice research projects.

Methods Employed: A series of factorial designed feeding trials are conducted to ascertain the effect of varying dietary concentrations of nutrients or different or different feed ingredients on growth, reproduction, and maintenance of rats, mice, or guinea pigs maintained in convention or specific pathogen-free environments. Criteria of evaluation include number of pregnancies, number of litters born and weaned, number of pups born and weaned, preweaning mortality, weight of offspring weaned, and the postweaning growth of offspring. Diets for maintenance are evaluated by determining longevity. Methods for improving diet palatability are also evaluated. Data from all studies are coded for computer analysis by the appropriate statistical methods.

Major Findings: This program has resulted in the development of open formula diets which are presently being fed to all small animal species throughout the NIH and the biomedical research community. Introduction of these diets to NIH has resulted in the procurement of animal feeds in full compliance with the Federal Procurement Regulations and has resulted in approximately 30 percent savings in the cost of procuring these commodities. During the development of these diets data have been generated to show nutrient requirements differ among various strains of small laboratory animals. These data have also been used by a committee of the National Research Council as the basis for estimating the quantitative nutrient requirements for the various species. Results from this program has also indicated purified diets and diets made only of ingredients of plant sources can be formulated to maintain mice for long-term experiments. The overall progress of this program has been inhibited as a result of delays in renovations in a new animal facility.

Significance: The efficiency of maintaining production and research colonies of laboratory animals can be markedly improved when diets supply nutrient concentrations equal to the actual requirements of the animal species involved. Diets formulated to accommodate specific research projects, or standard diets, provide NIH investigators and the scientific community with an essential research tool when experimental data are to be verified by replicating experiments. The use of open formula diets for large animal colonies also result in a considerable economic advantage for colony maintenance.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 0004-19 VR

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Tyzzer's Disease

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. R. Ganaway	Chief, Microbiology Unit	CPS VRB DRS
OTHER:	T. H. Spencer	Microbiologist	CPS VRB DRS
	A. M. Allen	Chief, CPS	CPS VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.7	PROFESSIONAL: 0.3	OTHER: 0.4

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The continuing purpose of this project is the study of Tyzzer's disease. The topics of present interest are: (1) characterization of the causative agent, Bacillus piliformis of which we presently have isolants from five animal species (rabbit, horse, rat, gerbil and mouse) in pure culture; (2) the serological response of the host to B. piliformis infection and the serological relationship between isolants from different animal species using the complement fixation test and fluorescent antibody techniques; (3) the pathogenesis of Tyzzer's disease in various animal species; and (4) the epidemiology of Tyzzer's disease, the goal being to identify primary sources of the infection.

Objectives: To characterize the etiologic agent, *B. piliformis*; to study the pathogenesis, the immune response and mechanisms, and to develop means to prevent or control the disease.

Methods Employed: Microbiology, immunology and pathology.

Major Findings: Indirect fluorescent antibody studies using immune sera prepared in rabbits against each of four animal specie isolants suggest that the isolants are related antigenically but are not identical. Survey of rat sera from several colonies with various types of colony management (e.g. germfree, barrier, conventional, etc.) indicate that *B. piliformis* infection is either an extremely common subclinical condition in rats or that *B. piliformis* is serologically related to some as yet unknown bacterium which is common in rats. A study of susceptibility of several inbred mouse strains to *B. piliformis* infection suggests that B-cell function rather than T-cell functions is associated with resistance. These studies also indicate that the B-cell deficient mouse (CBA/N, C3.CBA/N, Nu/+/Xid, or Nu/Nu-Xid/Xid) might be useful as sentinel animals or as agents for primary isolation of *B. piliformis*.

Significance: Often occurring as an epizootic, Tyzzer's disease causes fatal disease in mice, rats, hamsters, gerbils, laboratory rabbits, guinea pigs, nonhuman primates, cats, dogs, horses, wild hares, cottontail rabbits, coyotes, and muskrats. The etiologic agent, a Gram-negative, spore-forming, obligate intracellular parasite, is unique in the field of microbiology and remains unclassified. The disease occurs throughout the world and is one of the more important diseases of laboratory animals that interferes with and complicates biomedical research.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00011-06 VR

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Effect of Season on Pituitary and Gonodal Hormone Levels in Adult Male Macaques

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D.K. Johnson	Chief, VMSS	VRB DRS
	G.D. Hodgen	Chief, ES	RRB NICHHD

COOPERATING UNITS (if any)

Section on Endocrinology, Reproduction Research Branch, NICHHD

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 1.25	PROFESSIONAL: .25	OTHER: 1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objective of this study is to assess the seasonal changes in endocrine parameters important in male fertility. Measurements of androgens measured as a biorhythm will be correlated to breeding efficiency and season.

PHS-6040
(Rev. 10-76)

Objectives: In most studies of infertility, the major emphasis of investigation is on the female. This study encompasses a longitudinal analyses of fertility in the male rhesus monkey, *Macaca mulatta*, to investigate cyclic patterns of spermatogenesis.

Methods Employed: Ten male breeder monkeys were bled the first five days of each month for a 12-month period. Follicle-stimulating hormone, luteinizing hormone, testosterone, and androsterone were assayed using sensitive radioimmunoassay methods. The results were correlated with time of month, season, and breeding efficiency. Repeated blood samples are being taken to verify accuracy of radioisotope analyses of frozen serum.

Significance: Fertility and sterility studies focusing on male endocrine parameters have not been extensive. Approaching male endocrine changes as a biorhythm may lead to basic understanding of reproductive endocrinology. In addition, our results may be applied directly to biomedical research to improve nonhuman primate breeding, which is important because large-scale domestic colonies are a major resource to the scientific community.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00015-04 VR

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)
Defining the Nude Mouse Model

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.A. Whitney, Jr.	Chief	VRB DRS
Others:	C.T. Hansen	Geneticist	VRB DRS
	J.R. Ganaway	Chief, MU, CPS	VRB DRS
	A.M. Allen	Chief, CPS	VRB DRS
	H.J. Alter	Blood Bank	CC
	P. Holland	Blood Bank	CC
	R. Purcell		LID NIAID

COOPERATING UNITS (if any)

Laboratory of Infectious Diseases, NIAID
Blood Bank, Clinical Center

LAB/BRANCH
Veterinary Resources Branch

SECTION
N/A

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The nude mouse CBA congenic backcross was exposed to human viral hepatitis A. No signs of disease or indications of infection were identified. Because of other priorities this project will not be continued.

PHS-6040
(Rev. 10-76)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00016-04 VR

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Characterization of a New Viral Disease of Rabbits

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.D. Small	Animal Disease Investigator	VRB	DRS

COOPERATING UNITS (if any)

The Johns Hopkins University School of Medicine, Baltimore, Maryland

LAB/BRANCH
Veterinary Resources Branch

SECTION
Small Animal Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 1.0	PROFESSIONAL: 1.0	OTHER: 1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The initial phase of this project has been completed. The virus has been identified as a coronavirus which reacts with human coronaviruses OC43 and 229E. The virus causes lesions in the cardiac muscle (Cardiomyopathy) leading to right-sided failure and pulmonary edema. Rabbits, but not mice, hamsters, or guinea pigs are affected. Natural spread of the infections was not recognized. Results have been published.

Further work has been suspended pending availability of space.

PHS-6040
(Rev. 10-76)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00019-04 VR

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Aging Studies on HSR-Stroke/Prone Rats

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G. L. Clarke	Head, Pathology Unit	CPS VRB DRS
OTHER:	C. E. Hunt	Veterinary Pathologist	U. of Alabama

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.7	0.2	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objective is to determine the nature and incidence of pathology lesions that develop throughout the life span of HSR/stroke prone rats. WKY rats will be used as controls. Animals of each sex will be examined at 3 months, 6 months, 9 months, 12 months and 15 months of age. Tissues will be studied by light microscopic methods and if indicated, electron microscopic technique. These strains have great potential as animal models for the study of cerebrovascular disease in human beings.

PHS-6040
(Rev. 10-76)

Objectives: To determine the nature and incidence of pathologic lesions that develop throughout the lifespan of HSR-stroke prone rats. HSR-stroke prone rats are reported to be hypertensive, +140 mm Hg, but a pathologic study of the strain apparently has not been made. The HSR-stroke prone rat is reported to spontaneously develop cerebral infarcts, although documentation is sketchy. The WKY is the parent strain of the HSR and HSR-stroke prone rats and will be studied as a control.

Methods Employed: Animals of each sex will be selected for long-term holding. Aliquots will be killed at 3 months, 6 months, 9 months, 12 months and 15 months of age. Tissues will be studied by light and if indicated electron microscopic methods. Pathology will be correlated with lipoprotein and plasma triglyceride levels. WKY rats will be used as controls.

Significance: This strain has great potential as an animal model for the study of cerebrovascular and hypertensive disease in humans. Its value depends on accurate pathological description and documentation.

Proposed Course: Discontinued due to retirement.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00022-04 VR

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Skeletal Age Development in Macaca mulatta

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M. Michejda	Comparative Anatomist, VMSS	VRB DRS
	W. Watson	Chief, SAS	VRB DRS
	R.L. Killens	Chief, CMU, VMSS	VRB DRS
	J.D. Bacher	Chief, SU, VMSS	VRB DRS
	N.R. Hayes	Deputy Chief, VMSS	VRB DRS
	D.K. Johnson	Chief, VMSS	VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.0	1.0	2.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The most widely used methods (dental age, body weight) for age estimation in nonhuman primates are inadequate. More precise standards and age indicators are needed and can be obtained by measuring skeletal age, which has proven to be the best criteria for assessment of chronological age. Our longitudinal radiographic studies will provide information on the development and bone maturation of the hand and wrist in Macaca mulatta monkeys. The data will cover the entire period of appendicular bone maturation, from 120 days of gestation (the onset of carpal center ossification) to adulthood (over five years). To obtain the fetal data, a novel surgical technique of multiple uterotomies was developed. Serial radiographic data are obtained at three uterotomies and after delivery. The pre and postnatal age indicators will be prepared for publication as an atlas, which should make the data readily usable in many studies where the precise age of the experimental animal is required.

Objective: To provide information on bone development and maturation of the hand and wrist in the rhesus monkey, Macaca Mulatta. This information will be used for publication as an atlas and will serve as a comparison with human bone maturation.

Significance: Assessment of bone maturation by use of roentgenograms of the extremities is the best method for determining age. It provides age estimates throughout the developmental period and allows detection of experimentally induced variations in the skeletal development. Our data, obtained from normal fetuses, will be valuable for a variety of studies. The most important impact of it might be on experimental teratology and genetics, where rhesus monkeys of unknown age are widely used as models. It should constitute an important contribution to better understanding of prenatal development in Macaca mulatta. The data may also serve as a basis for comparison with human material in a variety of studies. Moreover, the sucess of the serial uterotomies may provide new possibilities for prenatal treatment of the human fetus, as for blood disorders when prenatal transfusion is needed but existing methods are risky; for skeletal disorders when early surgical treatment may be of great value; and, perhaps, for many other conditions that might be corrected by a surgical procedure before birth.

Proposed Course: Paper has been published.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00024-04 VR

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)
Anthelmintic Effect on Antibody Levels Following Primary and Secondary Immune Stimulation

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M.L. Morin	Chief, PRU, VMSS	VRB DRS
	G.D. Hodgen	Chief	ES NICHHD
	L.D. Stuart	Chief, UU, ACS	VRB DRS
	F.J. Judge	Chief, ACS	VRB DRS

COOPERATING UNITS (if any)
Section on Endocrinology, Reproduction Research Branch, NICHHD

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section and Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .01	PROFESSIONAL: .01	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this study is to determine if anthelmintics (thiabendazole or leavamisole hydrochloride) interfere with the normal immune response. Sheep receiving primary or secondary immune stimulation are being routinely dewormed, and the circulating antibody responses determined. Preliminary results indicate that the anthelmintics do not affect antibody production.

PHS-6040
(Rev. 10-76)

Objectives: The objective is to determine if anthelmintics (thiabendazole and levamisole hydrochloride) interfere with normal immune response as measured by circulating antibody levels.

Methods Employed: Sheep receiving primary or secondary immune stimulation were routinely dewormed, and the circulating antibody responses determined. Sheep were separated into three groups, one for each anthelmintic and one for saline control.

Major Findings: The information indicated that the drugs do not affect circulating antibody levels.

Significance: Findings indicate that routine deworming practices do not affect the immunologic response of antibody-producing ruminants.

Proposed Course: Discontinued.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00027-03 VR

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Linkage Analysis in the Laboratory Mouse

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	H. A. Hoffman	Chief, Genetics Unit	CPS VRB DRS
	J. S. Crowell, Jr.	Staff Fellow	CPS VRB DRS
	K. P. Smith	Geneticist	CPS VRB DRS
OTHER:	A. H. Grier	Biologist	CPS VRB DRS
	A. V. Williams	Biologist	CPS VRB DRS

COOPERATING UNITS (if any)
Cell Surface Antigen Laboratory, Memorial Sloan-Kettering Cancer Center, New York, New York; NIAID; and University of Melbourne, Australia

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.2	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project is designed to identify and locate on the chromosomes of the laboratory mouse inherited characteristics which can be used in a wide range of biomedical research. The areas of interest are: (1) characterization of the genetic trait by biochemical and immunological techniques; (2) chromosome mapping by standard genetic analysis; and (3) application of the genetic characteristics to explore new animal models of pathogenesis.

PHS-6040
(Rev. 10-76)

Objectives: To identify and locate on the chromosomes of the laboratory mouse genetic traits which can be used in a wide range of biomedical research areas.

Methods Employed: Analysis of proteins and enzymes by starch-gel electrophoresis complement and serum proteins by agar-gel double diffusion (Ouchterlony Analysis) and immunoelectrophoresis; and cell surface alloantigens by cytotoxic and immunofluorescence methods.

Major Findings: (1) Biochemical Markers: A detailed linkage analysis is being performed to determine the exact distance of the enzyme catalase from the loci coding for the major histocompatibility complex and thymic leukemia antigens in the mouse. There is some suggestion that recombination may be suppressed in this critical region of the seventeenth chromosome. (2) Lymphocyte Cell Surface Antigens: (a) A 4-point linkage analysis to determine the exact location of Ly-5 on chromosome 1 has been successfully complete and a manuscript is in preparation. Linkage studies on Ly-9 and Ly-6 are continuing. (b) Four congenic lines of mice with a C57Bl/6 background have been produced. One line carriers the TL^a and $Ce\text{-}2^b$ alleles on chromosome 17, while another congenic has the $Pep\text{-}3^b$ and $Ly\text{-}5^b$ alleles on chromosome 1. Two line congenic to Mup-1 and Lyb-2 on chromosome 4 also have been produced.

Significance: Determination of the chromosome location of these inheritable markers would permit their use in the quality control program initiated by the Genetic Monitoring Laboartory. In addition, these findings are of interest to the biomedical community with regards to the genetic characteristics of normal and diseased status.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00029-03 VR

PERIOD COVERED
October 1, 1979, to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Clinical Pathology Studies of Animal Health Conditions

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E. J. Baas	Chief, CU	VRB DRS
Other:	F. J. Judge	Chief, ACS	VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.5	PROFESSIONAL: 0.3	OTHER: 0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Studies are being conducted to define and characterize spontaneous diseases occurring in the NIH canine colonies. Preliminary clinical investigation has identified some disease problems. Hematological and chemical tests are being performed. The purpose of these investigations is to improve the quality of animals and animal products provided for research and characterize models of disease.

Objective: The objectives are to identify causes of diseases in NIH dog colonies, help determine the pathogenesis, improve the quality of animals and animal products provided, and characterize models of disease.

Methods Employed: Several standard hematological, and chemical procedures are being employed at the Animal Center and through commercial laboratories. When an unusual technique or information is needed, assistance is enlisted from various institutions.

Major Findings: The findings in anemic blood donor dogs indicate that iron deficiency is important in some dogs but other deficiencies such as vitamin deficiencies have major contributory roles.

Significance: It is necessary to identify the disease problems and control or eliminate them to provide improved animals and products for biomedical research. Complete characterization of some conditions may provide models of human conditions, or help illustrate the pathogenesis of animal diseases.

Proposed Course: Indefinite/continuing.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00030-03 VR

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Evaluation of _Mycobacterium_ _paratuberculosis_ Bacterin in the Goat

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M.L. Morin	Chief, PRU, VMSS	VRB DRS
	L.D. Stuart	Chief, UU, ACS	VRB DRS
	R. Merkal	Research Veterinarian	NADL

COOPERATING UNITS (if any)
National Animal Disease Laboratory, Agriculture Research Services, Ames, Iowa

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section and Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.02	.01	.01

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This study is designed to determine if a bacterin against _Johne's disease_ will affect the incidence and age of onset of the disease in goats. One-half of the kid _goats_ produced by Animal Center Section conventional does will be vaccinated at one month of age and observed for life.

PHS-6040
(Rev. 10-76)

Objectives: The objective is to determine if a bacterin against Johne's disease will affect the incidence and age of onset of the disease in goats.

Methods Employed: One-half of the kid goats produced by Animal Center Section conventional does will be vaccinated at one month of age with a whole-cell bacterin against *Mycobacterium paratuberculosis*. The other half (in most cases the twin) will be used as a control. The animals will be housed on contaminated pastures and will serve as usual in NIH programs. Animal cultures will be prepared to check for *M. paratuberculosis*. At the end of their usefulness or when they develop clinical Johne's disease, the goats will be necropsied and their Johne's disease status evaluated.

Major Findings: Findings will not be known until 1982.

Significance: With the use of a bacterin, it may be possible to prevent or delay the onset of Johne's disease in goats, as it is in cattle, thus enhancing the usefulness of goats in research.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00031-03 VR

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Serum Hormone Levels in Feral Pregnant Rhesus Monkeys

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M.L. Morin	Chief, PRU, VMSS	VRB DRS
	D.M. Renquist	Chief, PQU, ACS	VRB DRS
	G.D. Hodgen	Chief, ES	RRB NICHHD

COOPERATING UNITS (if any)

Endocrinology Section, NICHHD

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section and Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .01	PROFESSIONAL: .01	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this study is to observe the changes in reproductive hormone levels in feral pregnant rhesus monkeys. These changes may explain the high incidence of abortion during the first month of quarantine. Also, information on hormone levels during gestation in feral rhesus monkeys will be compared with data obtained from laboratory-bred monkeys.

PHS-6040
(Rev. 10-76)

Objective: The objective is to observe the changes in reproductive hormone levels in feral pregnant rhesus monkeys.

Methods Employed: Adult female rhesus monkeys are examined for pregnancy when they arrive at our facilities. Pregnant animals are bled three times per week until the pregnancy is terminated by abortion or parturition. Estrogen and progesterone levels are measured in each serum sample.

Major Findings: The data indicated only that an abortion had occurred but did not explain why or give advanced warning.

Significance: The results may explain the high incidence of abortion during the first month of quarantine. The hormone levels of feral rhesus monkeys during gestation will be compared with similar data from laboratory-bred rhesus monkeys.

Proposed Course: Discontinued.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00032-03 VR

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)
The Effect of Dietary Crude Fiber on the Digestibility of Proteins, lipids, and Carbohydrates in Macaca mulatta

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Dennis Barnard	Biol. Lab. Tech.	VRB DRS
Other:	D. M. Renquist	Chief, PQU, ACS	VRB DRS
	M. L. Morin	Veterinarian	VRB DRS
	J. Knapka	Nutritionist, SAS	VRB DRS

COOPERATING UNITS (if any)
Small Animal Section, VRB, DRS

LAB/BRANCH
Veterinary Resources Branch

SECTION
Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.10	.05	.05

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this study is to determine the digestibility coefficients of lipids, proteins, and carbohydrates as affected by different levels of crude fiber in monkey diets. The study involves comparing baked, 5.6 percent crude fiber diet to baked and extruded, standard diets containing about 3 percent fiber. The Feces from 12 monkeys fed the three diets were analysed for their digestibility coefficients.

PHS-6040
(Rev. 10-76)

Objectives: The purpose of the study is to determine the digestibility coefficients of lipids, proteins, and carbohydrates as affected by different concentrations of crude fiber in the nonhuman primate diets.

Methods Employed: Twelve rhesus monkeys, acting as their own controls, were fed experimental baked diets calculated to contain 2.9 percent and 5.6 percent crude fiber and a commercial extruded diet calculated as containing 2.5 percent crude fiber. Their feed intake and fecal output were determined. The Feces were analyzed to determine the digestibility coefficients.

Major Findings: Results indicate that the dietary crude fiber concentration used had no significant effect on the digestibility of crude protein and crude fat. The carbohydrate digestibility was significantly reduced when the 5.6 percent fiber diet was eaten. Crude fat and acid detergent fiber (ADF) digestibility were significantly different for baked and extruded diets. The ADF digestibility probably indicates the rhesus monkey has cellulolytic gut flora. The study also indicates that not only the quantity but also the quality of the dietary fiber is an important influence on the digestion of other nutrients.

Significance: This study follows up the Dietary Fiber Level Study (Z01 00023-01 VR). It is important to understand what portions of the crude fiber (insoluble carbohydrate and lignin) are digestible and how varying the crude fiber level affects the digestibility of lipids, proteins, and carbohydrates.

Proposed Course: A paper has been prepared for publication. The measurement of the fecal transit time using carmine as an indicator was not successful; radio-opaque pellets will be used in the future.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00033-03 VR

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Application of Automatic Data Processing to Nonhuman Primate Colony Management

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D. M. Renquist	Chief, PQU	VRB DRS
Others:	R. Van Wey, Jr.	MAO	OD DRS
	P. Basa	Computer Programmer	DCRT
	D. Burns	NAO	OD, DRS

COOPERATING UNITS (if any)

Division of Computer Research and Technology

LAB/BRANCH
Veterinary Resources Branch

SECTION
Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .20	PROFESSIONAL: .10	OTHER: .10

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Systems are being developed to computerize basic information obtained from nonhuman primates during the quarantine period (and in contract breeding operations). The systems will be used to provide clinical histories, morbidity and mortality data, drug treatment effectiveness and other information on either a colony or an individual basis. The system will ultimately be able to provide investigators with a complete clinical profile on monkeys issued by PQU and an inventory tracking system on primate breeders.

Objectives: The objective is to computerize basic information obtained from nonhuman primates during the quarantine period and in contract breeding operations.

Methods Employed: All routine background information including daily clinical history, diagnosis, and treatment data is computer entered on forms or by CRT. After issue of the animal the form is key punched and the data is stored for computer retrieval for quarantine purposes. The CRT program or "Primus" system is utilized for contract breeders.

Major Findings: All data have been placed in a historical archive file. Quarterly morbidity and mortality reports are received by disease, treatment, and cause of death. Epidemiologic and informational surveys on drug efficacy, disease spread, and inventory management can be provided.

Significance: The system will be used to provide clinical histories, morbidity and mortality data, drug treatment effectiveness, inventory tracking and other information on either a colony or individual basis.

Proposed Course: Indefinite

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00034-03 VR

PERIOD COVERED
October 1, 1979, to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Reproductive Physiology of Selected Exotic Nonhuman Primates

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D. M. Renquist	Head, PQU	VRB DRS
Others:	D. Wildt	Staff Physiologist	VRB DRS
	Dennis Barnard	Biol. Lab. Tech.	VRB DRS
	P. Chakraborty	Staff Physiologist	VRB DRS
	T. L. Wolfle	Asst. Head, CU	VRB DRS

COOPERATING UNITS (if any)

Reproductive Physiology Group, VRB

LAB/BRANCH
Veterinary Resources Branch

SECTION
Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.6	PROFESSIONAL: 0.2	OTHER: 0.4

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this study is to establish breeding systems for producing healthy, Aotus, Saimiri, Saguinus, and Cercopithecus in a consistent manner for research investigators at NIH and other interested scientists. Basic reproductive parameters being studied include duration of gestation, male and female reproductive cycles, accessory sexual organ development, male-female breeding ratios, reproductive hormone serum levels, puberty changes, infant development, and minimum reproductive age.

PHS-6040
(Rev. 10-76)

Objective: *The objective of the study is to establish breeding systems for producing healthy nonhuman primates.

Methods Employed: *Data will be collected for the following parameters: a) duration of gestation, b) male and female reproductive cycles, c) development of accessory sexual organs, d) male to female breeding ratios, e) reproductive hormone serum levels, f) puberty changes, g) infant development, and h) minimum reproductive age.

Major Findings: *Weights and measurements are being performed weekly on every owl monkey born to establish indices for normal development. To date ten animals are on the study. Weights at 6 months of age are between 402 and 563 grams, approximately one-half that of the adult. Deciduous tooth eruption patterns are similar to other nonhuman primates.

Significance: *This study will increase reproductive information to provide effective laboratory rearing of exotic nonhuman primates.

Proposed Course: *Indefinite/continuing

*See subprojects - Z01 RS 00051-01
and Z01 RS 00050-01 VR

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00036-03 VR

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Genetic Profile of the NIH Inbred Mouse Strains

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	H. A. Hoffman	Chief, Genetics Unit	CPS VRB DRS
	K. P. Smith	Geneticist	CPS VRB DRS
	J. S. Crowell, Jr.	Staff Fellow	CPS VRB DRS
OTHER:	A. H. Grier	Biologist	CPS VRB DRS
	A. V. Williams	Biologist	CPS VRB DRS

COOPERATING UNITS (if any)

Small Animal Section; VRB; DRS

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.5	PROFESSIONAL: 0.2	OTHER: 0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project is designed to identify and locate on the chromosomes of the laboratory mouse inherited characteristics which can be used in a wide range of biomedical research. The areas of interest are: (1) characterization of the genetic trait by biochemical and immunochemical techniques; (2) chromosome mapping by standard genetic analysis; and (3) application of the genetic characteristics to explore new animal models of pathogenesis.

PHS-6040
(Rev. 10-76)

Objectives: To identify and locate on the chromosomes of the laboratory mouse inherited traits which can be used in a wide range of biomedical research.

Methods Employed: Analysis of isozymes by starch-gel electrophoresis; complement and serum proteins by agar-gel double diffusion (Ouchterlony Analysis) and immunoelectrophoresis; and cell surface alloantigens by cytotoxic methods.

Major Findings: Forty-five inbred strains and substrains of laboratory mice have been characterized for 37 inherited traits. These genetic markers are distributed on 15 of the 19 autosomal chromosomes.

Significance: The genetic profile will make it possible to monitor inbred mice for their genetic integrity. It is of paramount importance that the genetic integrity of these strains be assured due to their universal use in the biomedical community. The genetic information obtained will also make these strains more useful as animal models to the biomedical community.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00037-03 VR

PERIOD COVERED
October 1. 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Fetal Surgery in the Macaca mulatta

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M. Michejda	Expert Consultant, VMSS	VRB DRS
	J.D. Bacher	Chief, SU, VMSS	VRB DRS

COOPERATING UNITS (if any)

Comparative Medicine Unit, VMSS
Primate Research Unit, VMSS

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .4	PROFESSIONAL: .2	OTHER: .2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Multiple uterotomies on pregnant rhesus monkeys are being done to expose the carpus or fetuses ranging in age from 120 to 163 days of gestation. The surgical procedure is being performed to establish an atlas for estimating skeletal age of the rhesus monkey before birth.

PHS-6040
(Rev. 10-76)

Objective: The aim of this project is to describe the surgical procedure used and to evaluate the effect of multiple uterotomies on pregnant rhesus monkeys.

Methods Employed: Multiple uterotomies were performed in sixty timed-pregnant monkeys on alternate weeks starting at 120 or 127 days of gestation to expose the carpus of the fetal monkey. Anesthetic techniques, postoperative care, and the effect of an antiabortive medication (Vasodilan) were evaluated in this group of females.

Major Findings: While monkeys are anatomically similar to man, they abort more frequently, particularly after intrauterine surgery. At the beginning of the study, a relatively high incidence of abortion led to improvement of the standard surgical procedures and postoperative care. Oxygen flow rates were increased from one to two liters per minute, the use of heating lamps was prolonged (minimum 48 hours postoperative), and the administration of antiabortive medication (Vasodilan 10 mg) became standard postoperative procedure.

Significance: Current antenatal surgical procedures (in man) are presently used chiefly for diagnostics. Those used most frequently are amniocentesis, amniography, fetography, fetal skin biopsy, and fetal blood transfusions. Fetal and maternal risks are high in antenatal surgery and further improvement of techniques is needed.

Proposed Course: Paper has been published.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00038-02 VR

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Linkage Analysis in the Laboratory Rat

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	K. P. Smith	Geneticist	CPS VRB DRS
	H. A. Hoffman	Chief, Genetics Unit	CPS VRB DRS
	J. S. Crowell, Jr.	Staff Fellow	CPS VRB DRS
OTHER:	A. H. Grier	Biologist	CPS VRB DRS
	A. V. Williams	Biologist	CPS VRB DRS

COOPERATING UNITS (if any)

Small Animal Section; VRB; DRS

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	1.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objective of this project is to develop a chromosome map for the laboratory rat. The project is designed to identify inherited characteristics of the laboratory rat which can be used in a wide range of biochemical research. The primary areas of interest are: (1) characterization of the genetic trait by biochemical and immunochemical techniques; (2) development of the chromosome map by standard genetic analysis; and (3) application of the revealed knowledge of the genetic characteristics to the exploration of new animal models of pathogenesis.

PHS-6040
(Rev. 10-76)

Objectives: The primary objective is to identify inherited characteristics of the laboratory rat. The genetically variable traits will be used to develop a chromosome map and a genetic profile of the laboratory rat.

Methods Employed: The primary methods of analysis are: (1) isozymes by starch-gel electrophoresis; (2) complement and serum proteins by agar-gel double diffusion (Ouchterlony Analysis) and immunoelectrophoresis; and (3) cell surface alloantigens by cytotoxic methods.

Major Findings: A new polymorphism was found for peptidase and the strain profiles were determined for all 26 inbred strains. Special matings were set up for the production of F_1 hybrids and backcrosses for the genetic analysis of the linkage data. The isozyme pattern for the F_1 hybrid exhibited the expected F_1 phenotypic pattern.

Significance: The development of a chromosome map is much like putting together a jigsaw puzzle, the more traits which are already mapped the easier it is to map other traits. The linkage information from the backcross data presently being collected will make it possible to locate peptidase on the chromosme map. Once the location is determined it will make it easier to map other traits. Traits for which the genetic linkage is determined may also be used in the development of congenic strains.

Proposed Course: Continuation. Manuscript in progress.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00039-02 VR

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Genetic Profile of the NIH Inbred Laboratory Rat

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	K. P. Smith	Geneticist	CPS VRB DRS
	H. A. Hoffman	Chief, Genetics Unit	CPS VRB DRS
	J. S. Crowell, Jr.	Staff Fellow	CPS VRB DRS
OTHER:	A. H. Grier	Biologist	CPS VRB DRS
	A. V. Williams	Biologist	CPS VRB DRS

COOPERATING UNITS (if any)

Small Animal Section; VRB; DRS

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 2.0	PROFESSIONAL: 1.5	OTHER: 0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objective of this project is to develop a genetic profile for the laboratory rat. The project is designed to identify inherited characteristics of the laboratory rat which can be used in a wide range of biochemical research. The primary areas of interest are: (1) characterization of the genetic trait by biochemical and immunochemical techniques; (2) development of the chromosome map by standard genetic analysis; and (3) application of the revealed knowledge of the genetic characteristics to the exploration of new animal models of pathogenesis.

PHS-6040
(Rev. 10-76)

Objectives: The primary objective is to identify inherited characteristics of the laboratory rat. The genetically variable traits will be used to develop a chromosome map and a genetic profile of the laboratory rat.

Methods Employed: The primary methods of analysis are: (1) isozymes by starch-gel electrophoresis; (2) complement and serum proteins by agar-gel double diffusion (Ouchterlony Analysis) and immunoelectrophoresis; and (3) cell surface alloantigens by cytotoxic methods.

Major Findings: Twenty-four inbred strains and substrains have been characterized for ten inherited traits. A new polymorphism was found for peptidase and the strain profiles were determined. Strain profiles were obtained for three other traits which showed genetic variation. Genetic variation was not found among the remaining six traits which were analyzed. Three additional loci have been found during this year as having genetic variation among the strains. Two of these are esterases and one is a seminal vesicle protein. Data is not being collected on the strain profiles for these strains.

Significance: The genetic profiles will make it possible to monitor the inbred rat strains for their genetic integrity. It is of paramount importance that the genetic integrity of these strains be assured due to their universal use throughout the biomedical community. The genetic information obtained will also make these strains more useful animal models to the biomedical community.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00040-02 VR

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Genetic Profile of the NIH Inbred Guinea Pig Strains

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	H. A. Hoffman	Chief, Genetics Unit	CPS VRB DRS
	K. P. Smith	Geneticist	CPS VRB DRS
	J. S. Crowell, Jr.	Staff Fellow	CPS VRB DRS
OTHER:	A. H. Grier	Biologist	CPS VRB DRS
	A. V. Williams	Biologist	CPS VRB DRS

COOPERATING UNITS (if any)

Small Animal Section; VRB; DRS; and Frederick Cancer Research Center - NCI

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	0.5	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project is designed to identify and locate on the chromosomes of the laboratory guinea pig inherited characteristics which can be used in a wide range of biomedical research. The areas of interest are: (1) characterization of the genetic trait by biochemical and immunochemical techniques; (2) chromosome mapping by standard genetic analysis; and (3) application of the genetic characteristics to explore new animal models of pathogenesis.

Objectives: To identify and locate on the chromosomes of the laboratory guinea pig inherited traits which can be used in a wide range of biomedical research.

Methods Employed: Analysis of isozymes by starch-gel electrophoresis; complement and serum proteins by agar-gel double diffusion (Ouchterlony Analysis) and immunoelectrophoresis; and cell surface alloantigens by cytotoxic methods.

Major Findings: Strain 2 and strain 13 inbred guinea pigs can be differentiated by three genetic markers: tissue hexose phosphatase, erythrocyte catalase, and an alpha-globular serum protein.

Significance: The genetic profile will make it possible to monitor the inbred guinea pig strains for their genetic integrity. It is of paramount importance that the genetic integrity of these strains be assured due to their universal use in the biomedical community. The genetic information obtained will also make these strains more useful as animal models to the biomedical community.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00041-02 VR

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Cytogenetics of Laboratory Rodents

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	K. E. Breach	Cytogeneticist	CPS VRB DRS
OTHER:	H. A. Hoffman	Chief, Genetics Unit	CPS VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project is designed to characterize the chromosome banding of the major animal strains used in biomedical research. The project will incorporate chromosome identification with somatic cell hybridization which will help to identify new linkage relationships which cannot be obtained by standard genetic analysis.

PHS-6040
(Rev. 10-76)

Objectives: The introduction of cytogenetics into the NIH genetic monitoring program.

Methods Employed: Standard techniques of chromosome banding.

Major Findings: The establishment of laboratory protocols for chromosome identification from murine splenic lymphocytes and murine tissue culture cells.

Significance: Identify specific chromosome sets from interspecific hybrids and assign linkage groups to new genetic markers.

Proposed Course: Discontinued.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00042-02 VR

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Development of a Standard Strain of Mice for Pertussis Vaccine Bioassays

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	K. P. Smith	Geneticist	CPS VRB DRS
OTHER:	C. T. Hansen	Geneticist	SAS VRB DRS
	C. R. Manclark	Research Microbiologist	PB BOB FDA

COOPERATING UNITS (if any)

Pertussis Branch; Bureau of Biologics; FDA; SAS: VRB: DRS

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 2.0	PROFESSIONAL: 1.5	OTHER: 0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objective of this project is to develop a standard strain of mice to be used for pertussis vaccine bioassays. Two lines of mice have been selectively bred for their susceptibility and resistance to sensitization by the histamine sensitizing factor (HSF) of *Bordetella pertussis* and have been designated HSFS/N and HSFR/N. After 20 generations of selection, the ability to be sensitized by HSF in the HSFS/N line has increased to 70 percent, and in the HSFR has decreased to 0.5 percent. The two lines have been further characterized for 12 biochemical isozymes.

PHS-6040
(Rev. 10-76)

Objectives: The ideal animal model for biological assays would be a strain for which the dose-response relationship is accurately predictable within a given dose range. The objective of this project is to develop a strain of mice with predictable and stable characteristics for the control testing of pertussis vaccine and other biologics.

Methods Employed: From a base population of NIH Swiss Webster stock N:NIH (SW), two lines of mice were selectively bred for their susceptibility and resistance to sensitization by the histamine sensitizing factor (HSF) of *Bordetella pertussis* and were designated HSFS/N and HSFR/N respectively. Weanling mice were injected with a saline suspension containing one opacity unit of pertussis vaccine, after five days the mice were challenged with histamine diphosphate. A minimum of 12 offspring were tested in each generation from each breeding pair. Almost all deaths due to sensitization occurred within one hour of injection.

Major Findings: After 20 generations of selection, the ability to be sensitized to HSF in the HSFS/N line has increased from 31 percent in the base generation to 70 percent in generation 20, and in the HSFR/N line has decreased from 31 percent to 0.5 percent. The estimates of the realized heritability were 32 percent in the HSFS/N line and 22 percent in the HSFR/N line. The genetic profiles have been determined for both lines for 12 biochemical isozymes. There were phenotypic differences between the lines for two of the 12 loci tested.

All testing of the HSFS/N strain in the past has been with a standard vaccine. Preparations are now being made to use the HSFS/N strain in a testing program using unknown vaccines sent to BOB for biological testing. These same vaccines will also be tested using mice from the N:NIH(s) stock which are the traditional animals used for pertussis vaccine testing.

A manuscript has been recently published. Smith, K. P., Hansen, C. T., and Manclark, C. R. (1979). Selective breeding to establish a standard mouse for pertussis vaccine bioassay III. Characterization of HSFS/N mice. Proceedings of the International Symposium on Pertussis, November 1978, NIH, Bethesda, Maryland.

Significance: The mice from HSFS/N strain provide the biomedical research community with an animal model which is highly sensitive to the lethal effects of histamine and is easily immunized by pertussis vaccine. The genetic profiles for the HSFS/N and HSFR/N strains indicate that each is isogenic and the profiles can be used in the future to uniquely differentiate these strains from all other strains in case of possible future genetic contamination.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00043-02 VR

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)
Micromethods for Cytotoxicity Testing in the Laboratory Mouse

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. S. Crowell, Jr.	Staff Fellow	CPS VRB DRS

COOPERATING UNITS (if any)
None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.8	PROFESSIONAL: 0.8	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to develop techniques for rapidly typing the cell surface antigens expressed on lymphocytes from various strains of mice. A variety of methods using both vital dye exclusion and radioisotope release are being explored.

PHS-6040
(Rev. 10-76)

Objective: To develop a rapid, efficient, and accurate method for typing mouse lymphocytes.

Methods Employed: Several standard serological methods have been examined for their applicability to the routine needs of the genetic monitoring program.

Major Findings: A modification of the standard human leukocyte testing methods has been adopted for routine use. The majority of mouse strains maintained in the NIH colony have now been typed for a variety of cell surface antigens. Several strains developed within the colony appear to have recombinant phenotypes at the major histocompatibility locus (H-2); a fact that may be of considerable interest to investigators utilizing these animals.

Significance: Successful completion of this project will permit the Genetic Monitoring Program to test a large number of mice for inheritable traits with a minimum expenditure of time and funds. Interest in this project has been expressed by a number of other laboratories concerned with quality control in large mouse colonies.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00045-02 VR

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Flexible Fiberoptic Bronchoscopy of the Rhesus Monkey (Macaca mulatta)

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Ira J. Strumpf	Senior Staff Fellow	PB NHLBI
	John D. Bacher	Chief, SU, VMSS	VRB DRS
	James E. Gadek	Senior Investigator	PB NHLBI
	Martin L. Morin	Chief, PRU, VMSS	VRB DRS

COOPERATING UNITS (if any)

Surgery Unit, VMSS
Primate Research Unit, VMSS

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, MD 20205

TOTAL MANYEARS: .4	PROFESSIONAL: .3	OTHER: .1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this study is to develop an animal model for human emphysema. Under direct visualization through the bronchoscope, foreign or natural materials such as $C5_a$ or endotoxin will be installed into right lung.

The left lung will serve as a control. Weekly saline lavages for six weeks will be assayed for neutral proteinases, elastase, and alphal antitrypsin activity as determinates for the development of emphysema.

PHS-6040
(Rev. 10-76)

Objective: The aim is to produce a valid animal model for the study of human emphysema.

Methods Employed: A pediatric fiberoptic bronchoscope (O.D. 4.5. mm; length 605 mm) or an adult bronchoscope (O.D. 5.8 mm, length 605 mm) were used for inspection, saline lavages, and photography. After installation of various substances into the right lung, saline lavages using the adult bronchoscope are being done to determine if emphysema is developing.

Major Findings: The project is in the development stage.

Significance: The etiology of emphysema is still unknown. A good animal model is needed to effectively study this disease process.

Proposed Course: Completed

Strumpf, I.J., Bacher, J.D., Gadek, J.E., Morin, M.L., Crystal, R.G.: Flexible Fiberoptic Bronchoscopy of the Rhesus Monkey (*Macaca mulatta*). Lab Animal Sci 29(6): 785-788, 1979.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00046-02 VR

PERIOD COVERED
October 1, 1979, to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Evaluation of Donor Safety in Leukopheresis of Canines

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E. J. Baas	Chief, CU, ACS	VRB DRS
Other:	F. J. Judge	Chief, ACS	VRB DRS
	J. E. French	Research Physiologist	DBBP BoB
	J. C. Fratatoni	Director, BPB	DBBP BoB

COOPERATING UNITS (if any)
Blood Products Branch, Division of Blood and Blood Products
Bureau of Biologics, FDA

LAB/BRANCH
Veterinary Resources Branch

SECTION
Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.6	0.2	0.4

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Leukopheresis on canine blood donors is being conducted to determine if repeated removal of lymphocytes affects the immune response. Information obtained on the maximum frequency or total number of leukopheresis donations is to be extrapolated for human donors.

PHS-6040
(Rev. 10-76)

Objectives: The objective is to determine if frequent removal of lymphocytes will deplete their number or have a detrimental effect on the immune process.

Methods Employed: Foxhound blood donor dogs are being leukopheresed with a Haemonetics Model 30 Blood Processor using techniques for human donors. The lymphocytes are being separated and stimulated with mitogens to measure their ability to respond.

Major Findings: Improved methodology for dog lymphocyte collection has been developed. Preliminary findings indicate that the immune system may be affected by frequent lymphocyte collection.

Significance: There is a definite trend to regular and frequent granulocyte donations in human medicine. The effects on specific immune responses of the long-lived T lymphocyte are poorly understood. This study with the dog model will determine if there are definite detrimental effects from frequent donation.

Proposed Course: This project will serve as a basis for more comprehensive studies in humans and the canine model.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00047-02 VR

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Screening Laboratory Animal Diets for Chemical Contaminants

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.J. Knapka	Nutritionist	VRB	DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH

Veterinary Resources Branch

SECTION

Small Animal Section

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.25	0.01	0.24

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A program has been established for the routine analyses of feed samples for chlorinated hydrocarbons, polychlorinated biphenyls, organo-phosphates, lead, arsenic, cadmium, mercury, nitrate, and aflatoxins. Nitrosamines assays are being conducted on feed samples selected at random. The objective of this program is to document the concentrations of these potential contaminants in natural ingredient laboratory animal diets and to establish the maximal permissible concentrations that can be attained on a practical basis.

PHS-6040
(Rev. 10-76)

Objectives: To collect data regarding the concentrations of potential chemical contaminants in laboratory animal diets in order to obtain a basis for establishing maximum acceptable concentrations of these contaminants in diets for laboratory animals.

Methods Employed: Manufacturers of all NIH laboratory animal diets are required to collect representative samples of each production batch of diet. These samples are mailed to an independent laboratory where they are analyzed for chlorinated hydrocarbons, polychlorinated biphenyls, organo-phosphates, lead, arsenic, cadmium, mercury, nitrate, and aflatoxins under an NIH contract. In addition, diet samples are collected on a random basis in the NIH warehouse and mailed to a university laboratory for nitrosamines analysis. All assay results are mailed directly to the appropriate NIH personnel for evaluation.

Major Findings: Preliminary summaries of the monitoring results indicate there are extremely low concentrations of most contaminants in various batches of feed. However, there is a large amount of variation in the concentrations. There have not been sufficient numbers of samples analyzed to establish any trends or to ascertain the degree of errors due to sampling or analytical procedures associated with these results.

Significance: In recent years various NIH investigators have expressed concern regarding the potential effect residual concentrations of dietary chemicals can have on animals involved in various kinds of research. A major issue in this regard is lack of knowledge concerning the biological effect of low concentrations of dietary chemical contaminants. This program is designed to document dietary contaminant levels so these data are available for the evaluation of experimental data.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00048-01

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)
Synchronization of the Reproductive Cycle and Timed Ovulation and Mating of Macaca fascicularis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D.E. Wildt	Staff Physiologist, OC	VRB	DRS
Other:	D.M. Renquist	Head, PQU, ACS	VRB	DRS
	D. Barnard	ACS	VRB	DRS
	P.K. Chakraborty	Staff Physiologist, OC	VRB	DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Office of the Chief

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Hormonal control of the reproductive cycle of the Cynomolgus macaque is of particular interest in the development of timed-mating or embryo collection studies. In this investigation, which employs laparoscopic visualization of ovarian activity and radioimmunoassay of serum to confirm endocrine function, attempts are being made to synchronize female macaques to ovulate and breed at similar times. Progesterone is administered to mature animals disregarding the stage of its natural menstrual cycle. Following progesterone withdrawal, ovarian function is monitored serially in each animal by laparoscopy and assay of frequently obtained blood samples. At the appropriate time, females are paired with breeding males until ovulation and copulation are confirmed.

Objective: The objective is to test the synchronizing effect of daily progesterone treatment and withdrawal on subsequent ovulation and breeding time in the Cynomolgus macaque.

Methods: Adult Cynomolgus females are assigned to this study with no regard to either follicular or luteal phase status. Ovarian function before, during, and following exogenous progesterone treatment is monitored by laparoscopic observation of the ovaries and assay of sera for progesterone and estradiol titers. At a precise interval following daily administration of progesterone and then withdrawal, females are paired with males for a short, predetermined interval and later removed and monitored for pregnancy.

Significance: The ability to synchronize a group of randomly cycling nonhuman primates to ovulate and mate over a predetermined shortened time interval could improve reproductive management efficiency within a breeding population. Of particular benefit would be those investigations concerned with obtaining nonhuman primate embryos of precise preimplantation stages of development for subsequent *in vitro* culture or transfer between animals. Furthermore, because ovarian observation and serum hormone data are being obtained prior to steroid treatment,the stage of menstrual cycle can be estimated. This will provide additional information on the existence of a difference in effect of progesterone administration given during either the follicular or luteal phase.

Proposed Course: This project has been initiated recently. Depending on the results, progesterone dosages or the injection regimen may be modified to determine the minimum treatment required to produce an effect.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00049-01 VR

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Sterilization of the Male Dog and Cat by Laparoscopic Occlusion of the Vas Deferens

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D.E. Wildt	Staff Physiologist, OC	VRB	DRS
Other:	S.W.J. Seager	Head, Reproductive Physiology Group, OC	VRB	DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Office of the Chief

INSTITUTE AND LOCATION
DRS, NIH, Building 14G, Room 102

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.1	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

There is little clinical data available on the use of alternative surgical techniques beyond castration for producing sterility in the male dog and cat. Furthermore, only limited data exist on the effect of vas deferens severance or blockage on the dog, and no information has been published on the effects of similar surgical procedures in the cat. In this study, a laparoscopic technique was developed to occlude the vas deferens in dogs and cats. The effects of this surgical procedure on pubertal onset, libido, sperm production, testicular volume, and general animal health has been investigated. Results indicated that there were no adverse effects resulting from laparoscopic vas occlusion with regard to onset of sexual activity or copulatory ability. Sperm counts in adult dogs and cats decreased to zero within two and five days, respectively. Histological examination demonstrated that spermatogenesis was normally active in all animals. Granuloma formation was confirmed in vas deferens biopsies in one-half the animals in each group, but this finding had no apparent compromising effect on general animal health.

Objective: The objective is to develop a laparoscopic sterilization technique and to evaluate the effects on various reproductive factors in the adult and prepubertal male dog and adult male cat.

Methods: Routine diagnostic laparoscopic procedures were used to visualize the intra-abdominal portions of the vas deferens in anesthetized prepubertal and adult dogs and adult male cats. Using an ancillary surgical forceps under laparoscopic visualization, a short segment of each vas deferens was electrocoagulated. Comparative controls underwent sham surgery. Pre and postlaparoscopy ejaculates were obtained and microscopically evaluated and, following sterilization, animals were monitored frequently for copulatory ability, alterations in testicular volume, and general animal health. Post-mortem examinations were conducted at 9 to 21 months following vas deferens occlusion.

Major Findings: Sperm counts in adult dogs decreased to zero within two days of treatment. There was a nonsignificant tendency for testes volume to decline following sterilization; however, this observation may have been seasonally related. Sterilization of prepubertal dogs resulted in chronic azoospermia without influencing body weight or testes development. This technique also resulted in zero sperm counts in adult cats. However, in some cats, at least several postoperative semen collections were necessary to eliminate live spermatozoa from the ejaculate. Testes volumes in cats were significantly increased following sterilization and appeared related to an increase in epididymal fluid retention that was observed at necropsy. Laparoscopic sterilization had no effect on libido. Although post-mortem examination revealed normal spermatogenesis, 33 percent of the test animals produced spermatocelic lesions and 50 percent produced granuloma formation in the reproductive tract. General animal health appeared unaffected.

Significance: Since laparoscopy has been used extensively as a minor invasive procedure to control fertility in women, its potential as a tool for sterilization in the dog and cat is of interest. The technique described in the present study was simple, safe, and effective resulting in rapid azoospermic with no apparent reduction in libido or maintenance of testicular integrity.

Proposed Course: Manuscript submitted for publication.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00050-01 VR

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)
Reproductive-Endocrine Studiies in the Laboratory Cat

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D.E. Wildt	Staff Physiologist, OC	VRB	DRS
	P.K. Chakraborty	Staff Physiologist, OC	VRB	DRS
Other:	S.Y. Chan	Postdoctoral Fellow, OC	VRB	DRS
	S.W.J. Seager	Head, Reproductive Physiology Group, OC	VRB	DRS
	S.J. O'Brien		LVC	C

COOPERATING UNITS (if any)
Laboratory of Viral Carcinogenesis, National Cancer Institute

LAB/BRANCH
Veterinary Resources Branch

SECTION
Office of the Chief

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.3	0.2	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The domestic cat serves as a valuable animal model in many biomedical fields including genetic, neural, ophthalmic, and metabolic research. However, controlled laboratory breeding of feline models is often unsuccessful, which is, in part, due to a paucity of information on the basic behavioral-reproductive patterns of cats maintained under laboratory conditions. The overall goal of this project is a series of comprehensive investigations concerning definition of ovarian, behavioral, and endocrine relationships in the domestic cat during prepuberty, estrus, pseudopregnancy, pregnancy, parturition, and the postpartum interval. To date, these correlates have been completely established for the estrous and pseudopregnancy intervals and are approaching completion for characterization of the pregnancy and parturition stages of reproduction. Baseline information obtained is being applied successfully to improve reproductive efficiency and breeding management within feline breeding colonies at NIH.

Objectives: This project, which is composed of a series of individual studies, each with specific goals, has a single overall objective: the definitive characterization of reproductive relationships in the female cat.

Methods: Laboratory maintained cats of various ages are assigned to specific studies with the following general interests: 1) onset of puberty and endocrine and ovulatory response at first estrus in young queens; 2) relationship of the number of copulatory stimuli and ovulatory-endocrine responses during estrus; 3) relationship of reproductive behavior, hormones, and ovarian activity during pseudopregnancy, pregnancy, parturition, and the postpartum interval. Data are obtained by frequent monitoring of sexual behavior, ovarian observation by laparoscopy and blood collection, and subsequent radioimmunologic assay for serum concentrations of estradiol, luteinizing hormone, and progesterone.

Major Findings: Although comprehensive evaluations have not been completed in some of the individual studies, data obtained indicates the domestic cat exhibits several reproductive functions apparently unique to this species. Although classified as an induced ovulator (i.e., copulation required for ovulation to occur), results demonstrated a different mating-ovulatory mechanism than traditionally reported for another common induced ovulator, the rabbit. Results showed that multiple matings at precise intervals in the cat are necesary to elicit a pituitary-hormonal reaction and subsequent ovulation. Endocrine response gradually declines as a result of repeated matings. These data have been valuable in performing timed matings and obtained pregnancies in feline animal models.

Significance: The domestic cat is used extensively as a laboratory model and serves the public as a valuable companion species. Yet compared to other common domestic species, comparatively little precise data have been published on reproductive relationships in the cat. These series of studies will provide a comprehensive understanding of reproductive control mechanisms, thus allowing improved breeding management for the production of feline research models.

Proposed Course: Continuation. Currently, one manuscript is accepted for publication and another is being prepared for submission.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00051-01 VR

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Reproduction in Mutant Corriedale Sheep Used as an Animal Model for the Study of Hyperbilirubinemia (Dubin-Johnson Syndrome)

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. Stuart	Chief, UU, ACS	VRB	DRS
	D.E. Wildt	Staff Physiologist, OC	VRB	DRS
Other:	S.C.Kalser	Liver Diseases Program Director	DDN	NIAID
	P.K. Chakraborty	Staff Physiologist, OC	VRB	DRS

COOPERATING UNITS (if any)

Digestive Diseases and Nutrition Program, National Institute of Arthritis, Metabolism and Digestive Diseases

LAB/BRANCH

Veterinary Resources Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.1	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A specific genetic strain of Corriedale sheep is used as an animal model for the study of liver pathophysiology, specifically, hyperbilirubinemia (Dubin-Johnson Syndrome). This project is concerned with increasing the numbers of animals available for research by the controlled breeding of individuals which genetically transmit this character. This project is utilizing what is considered to be the only existing Corriedale sheep homozygotic for this trait. Efforts are being made to obtain both homozygous and heterozygous offspring from these highly inbred individuals. This will allow perpetuation of this specific gene pool and ensure availability of research animals for future investigations of Dubin-Johnson Syndrome and related metabolic disorders.

PHS-6040
(Rev. 10-76)

Objective: The objective is to successfully breed and obtain offspring from a limited number of inbred Corriedale sheep which genetically transmit hyperbilirubinemia (Dubin-Johnson Syndrome).

Methods: A total of six (three rams, three ewes) inbred Corriedale sheep homozygotic for transmitting Dubin-Johnson Syndrome are availabe for use. Initially, standard breeding and management procedures will be employed. Homozygotic males will be naturally mated with both the homozygotic females and 12 outbred ewes. The latter successful breeding will result in a proportion of the offspring being heterozygotic for hyperbilirubinemia. Backcrossing or inbreeding of these animals can eventually also produce offspring homozygous for the metabolic disorder. In the event that natural breeding efforts are unsuccessful, hormonal manipulation of the reproductive cycle and artificial insemination with fresh or frozen spermatozoa will be considered. The goal for the first year is to produce one or two homozygotic and ten heterozygotic offspring.

Major Findings: This project has only recently been initiated.

Significance: Only a limited number of a specific strain of sheep now exists that genetically transmits a metabolic disorder which also occurs in man. This project attempts the controlled breeding of this small population in an effort to retain this particular gene pool and ensure the availability of research animals for future investigations.

Proposed Course: Continuation

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00052-01 VR

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)
Development of Embryo Collection, Freeze Preservation, and Transfer Capabilities in the Laboratory Mouse

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S.W.J. Seager	Head, Reproductive Physiololgy Group, OC	VRB	DRS
Other:	S.Y. Chan	Postdoctoral Fellow, OC	VRB	DRS
	P.K. Chakraborty	Staff Physiologist, OC	VRB	DRS
	D.E. Wildt	Staff Physiologist, OC	VRB	DRS
	R.A.Whitney, Jr.	Chief,	VRB	DRS

COOPERATING UNITS (if any)
None

LAB/BRANCH
Veterinary Resources Branch

SECTION
ffice of the Chief

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 1.0	PROFESSIONAL: 0.5	OTHER: 0.5

CHECK APPROPRIATE BOX(ES)
☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER
☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Numerous specific strains of laboratory mice are utilized as research models. However, immediate research needs for certain murine genetic types varies considerably. This often results in the excessive expense of maintaining many breeding animals from a certain strain which may or may not be valuable for future investigations. One alternative is the freeze preservation of embryos, which, at a later time, can be thawed and transferred to recipient dams, thus perpetuating specific strains. In this study the techniques necessary to collect, freeze, thaw, and surgically transfer mice embryos are being developed. Such procedures will eventually be used to more economically manage and store invaluable genetic stocks to ensure availability for future research investigations.

PHS-6040
(Rev. 10-76)

Objective: The objective is to develop methodology to effectively collect, freeze, thaw, and successfully transfer mouse embryos.

Methods: N:NIH(s) mice are being used to develop techniques. Immature mice are superovulated with a combination of gonadotropin injections and then mated with intact males. Females are then sacrificed at specific intervals after tbreeding and, using a stereomicroscope, the oviducts are flushed with media and examined for embryos and stage of their morphologic development. Embryos are then cultured and used to develop successful interanimal transfer or freeze preservation procedures.

Major Findings: During the formative months of this project, emphasis has focused on the establishment of a research mouse colony, the development of embryo collection and handling techniques, and the purchase and collection of necessary chemicals and equipment. A number of exogenous hormonal regimens for inducing superovulation have been tested. One, using pregnant mares' serum and human chorionic gonadotropin has been selected for consistently inducing increased ovulation rate and, thus, improving number of embryos collected per donor female. Various culture media and environments are being tested and successful culture of two-celled stage embryos to the eight-celled stage has been achieved.

Significance: In recent years, laboratory research has established the possibility of collecting early embryonic tissue, freezing such material and then obtaining live offspring following thawing and transfer of the embryos to recipient females. Such procedures would have considerable application to the maintenance and preservation of animal research models for human disease. Since numerous valuable strains exist and, since this species is easily handled and generally prolific, the mouse would appear to be an ideal candidate for testing the practical feasibiltiy of a large-scale embryo freezing program.

Proposed Course: Continuation

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00053-01 VR

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Characterization of the Antigenic Components Specific to the Canine and Feline Ovary

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P.K. Chakraborty	Staff Endocrinologist, OC	VRB	DRS
Other:	S.Y. Chan	Postdoctoral Fellow, OC	VRB	DRS
	D.E. Wildt	Staff Physiologist, OC	VRB	DRS
	A.P. Stewart	Laboratory Technician, OC	VRB	DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH

Veterinary Resources Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.7	PROFESSIONAL: 0.5	OTHER: 0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The antigenic components of canine and feline ovaries have not been investigated. It is of importance to characterize these components and identify any antigen that may be ovary specific. Such antigens can be a target for raising ovarian antibody and, thus, provide an immunologic method to control fertility in the unwanted pet population. Results have indicated that there is at least one ovary-specific antigen in the canine, and the antibody raised against it would specificially bind with both ovarian homogenate and isolated canine ovarian cells.

PHS-6040
(Rev. 10-76)

Objective: To identify and characterize the ovarian antigenic composition in the dog and the cat. To raise antibodies against such antigens and use these as a probe to investigate the immunological factors involved in the reproductive process in these two species. Such antibodies may ultimately prove useful in controlling reproduction in the unwanted pet population.

Methods Employed: Rabbits were immunized against ovarian homogenates and the antisera used to characterize antigens present in the ovaries. Double gel diffusion and immunoelectrophoresis were utilized to study the precipitin bands while binding of antibody to isolated ovarian cells was demonstrated by using the immunofluorescence technique.

Major Findings: Following purification of the antisera to remove non-specific antibodies, one antigen could be shown to be present that was specific to the canine ovary. No specific ovarian antigen has so far been detected in the cat.

Significance: These studies provide a way to investigate the immunological processes involved in the reproduction of the dog and the cat. Antisera raised against specific ovarian, luteal, or uterine antigens would serve as probes to investigate the fetus-dam relationship. Such studies may eventually lead to development of suitable vaccines to control unwanted pet population.

Proposed Course: Part of the work characterizing the antigenic characters of the ovaries has been reported in a doctoral thesis submitted to Baylor College of Medicine. One additional manuscript has been accepted for publication. Goats are at present being immunized against luteal antigens and these will be characterized in the future.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00054-01 VR

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Relationship of Growth Hormone and Growth in the Dog

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P.K. Chakraborty	Staff Endocrinologist, OC	VRB	DRS
Other:	S.W.J. Seager	Head, Reproductive Physiology Group, OD	VRB	DRS
	A.P. Stewart	Laboratory Technician	VRB	DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH

Veterinary Resources Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.1	0.05	0.05

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project was designed to examine the relationship between circulating levels of growth hormone and growth characteristics in the purebred Labrador bitch. Body weights were recorded at predetermined intervals and serum growth hormone concentrations were measured during this period of prepubertal growth. Data were converted to reflect actual body weight increments and linear correlation analyses were conducted with growth hormone as the independent variable. Serum growth hormone concentrations showed a biphasic profile as did body weight increments during the same period.

Objective: To determine if serum growth hormone levels are correlated with early growth in the bitch.

Methods Employed: A specific double antibody radioimmunoassay validated for canine growth hormone was utilized in this study. Body weight data was converted as a percent increment over the previous body weight using the formula $(w_2-w_1)/w_1 x100$; where w_1 is the previous body weight and w_2 is the present body weight.

Major Findings: Both serum growth hormone concentration and percent body weight increment showed a similar biphasic pattern with the lowest growth hormone level and growth increment recorded between 10-12 weeks of age. Increase in body weight was linear between 4-26 weeks of age and 99 percent of mature body weight was reached by 10 months of age.

Significance: This study defines body weight gains in terms of observed changes in growth hormone levels. It appears that these two factors are correlated during the early prepubertal growth. The data indicate that the period between 10-12 weeks of age may be a critical point during the growth of the dog.

Proposed Course: Complete. A manuscript is in preparation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00055-01 VR

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)
Ovulation Induction in the Anestrous Bitch

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P.K. Chakraborty	Staff Endocrinologist, OC	VRB	DRS
Other:	D.E. Wildt	Staff Physiologist, OC	VRB	DRS
	A.P. Stewart	Laboratory Technician, OC	VRB	DRS
	S.W.J. Seager	Head, Reproductive Physiology Group, OC	VRB	DRS

COOPERATING UNITS (if any)
None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Office of the Chief

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.2	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The duration of anestrus in the bitch is highly variable and can last from 4-12 months. It would be important to reduce this time period so as to increase reproductive potential. The present study was designed to develop an effective hormone regimen to induce estrous cyclicity before four months following the last known estrous cycle or whelping. Some of the anestrous bitches used in this study were monitored for changes in ovarian activity by laparoscopy before and after sequential treatments with estradiol, pregnant mare serum gonadotropin (PMSG), and human chorionic gonadotropin (HCG). Serum samples will be analyzed for estradiol, progesterone, and luteinizing hormone.

Objective: To determine the conditions appropriate for induction of [illegible] canine. This study is further designed to investigate the optimum dosage and regimen of hormonal therapy to induce follicular development, estrous behavior, ovulation, and pregnancy in the anestrous bitch.

Methods Employed: Laparoscopy is utilized to observe the ovarian and uterine morphology. Animals are treated with 100 micrograms of estradiol for three days followed by two injections of a combination of 1000 i.u. of PMSG and 500 i.u. of HCG, seven days apart. Animals were bred by artificial insemination three times during the period of estrus. Blood samples were collected during induced estrous cyclicity.

Major Findings: Results obtained so far indicate that pretreatment with estradiol for three to four days can induce luteolysis and cause sanguinous discharge typical of [illegible] in this species. Estrus subsequently developed in many bitches which were then [illegible]

Significance: This project investigates the efficacy of different hormonal regimens to induce estrous cyclicity during early anestrus in the bitch. Development of such a treatment can improve the reproductive efficiency of the bitch by more than 50 percent.

Proposed Course: Further work is in progress. Serum samples will be analyzed for concentrations of estradiol and progesterone. All whelping data will be analyzed and results of different treatment regimens will be compared statistically.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00056-01 VR

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)
Mandibular Analysis as a Means of Discriminating Inbred Strains of Mice and Rats

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	H. A. Hoffman	Chief, Genetics Unit	CPS VRB DRS
	K. P. Smith	Geneticist	CPS VRB DRS
OTHER:	A. G. Grier	Biologist	CPS VRB DRS
	A. V. Williams	Biologist	CPS VRB DRS
	H. Blum	Physical Scientist	LSM, DCRT
	J. Mosimann	Statistician	LSM, DCRT

COOPERATING UNITS (if any)

SAS; VRB; ORS; Laboratory Statistical and Mathematical Methodology, DCRT

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.4	PROFESSIONAL: 0.2	OTHER: 0.2

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The project is designed to determine the ability of the mandibular analysis to discriminate between inbred strains of mice and rats maintained by the VRB. Discriminant Analysis, Canonical Correlation Analysis, and Computer Image Analysis are being used to analyse data from 20 inbred strains of mice.

Objective: To evaluate [illegible]

[illegible]

Methods Employed: Analysis of data by Statistical Package for Social Sciences computer programs and computer image analysis.

Major Findings: Project in progress, no findings as of now.

Significance: The mandible could be used as a genetic character [illegible] can be used to screen a large number of mice for genetic [illegible]

Proposed Course: Continuation.

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